Micronutrient Information Center

The Linus Pauling Institute's Micronutrient Information Center is a source for scientifically accurate information regarding the roles of vitamins, minerals, phytochemicals (plant chemicals that may affect health), and other dietary factors, including some food and beverages, in preventing disease and promoting health. All of the nutrients and dietary factors included in the Micronutrient Information Center may be obtained from the diet, and many are also available as dietary supplements.

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About

Español

The Linus Pauling Institute's Micronutrient Information Center (MIC) is a source for scientifically accurate information on the functions and health effects of all micronutrients (vitamins and nutritionally essential minerals); other nutrients like choline and essential fatty acids; dietary factors, including many phytochemicals (non-nutritive plant chemicals that may affect health); and some food and beverages, including tea, coffee, and alcohol. All of the nutrients and dietary factors included in the MIC may be obtained from the diet, and many are also available as dietary supplements; dietary and supplemental sources are discussed in each article.

Human research is emphasized in the MIC, although cell culture or animal studies may be mentioned when human studies are lacking. Most MIC articles have summaries at the beginning and include the following subsections: Function or Biological Activities, Metabolism and Bioavailability, Deficiency, The RDA or AI (for males and females of various age groups), Disease Prevention, Disease Treatment, Sources (food and supplements), and Safety (toxicity and drug or nutrient interactions). For the micronutrients (vitamins and essential minerals), the Linus Pauling Institute provides a daily intake recommendation.

For each article, Ph.D. nutrition scientists critically review and synthesize basic, clinical, and epidemiological studies in the peer-reviewed literature and provide references throughout. Each article is then additionally reviewed by an expert in the field; the names of the authors and reviewers are listed at the bottom of each article. This multiple review process minimizes bias and presents objective information.

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We welcome your inquiries and feedback via email.

Journalists wishing to contact members of the Linus Pauling Institute can consult our media contact page. The Micronutrient Information Center staff can be contacted directly though email.

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We welcome your questions and comments, and will do our best to respond accurately and timely. As nutrition scientists (not medical doctors), we are unable to answer questions that relate to personal medical issues. Please contact us using the form below, and a MIC staff member will respond to you via email.

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Articles

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Vitamins

Español

The term vitamin is derived from the words vital and amine, because vitamins are required for life and were originally thought to be amines. Although not all vitamins are amines, they are organic compounds required by humans in small amounts from the diet. An organic compound is considered a vitamin if a lack of that compound in the diet results in overt symptoms of deficiency.

The information from the Linus Pauling Institute's Micronutrient Information Center on vitamins and minerals is now available in a book titled, *An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations*. The book can be purchased from the Linus Pauling Institute or Thieme Medical Publishers.

Select a vitamin from the list for more information.

- Biotin
- Folate
- Niacin
- Pantothenic Acid
- Riboflavin
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- Vitamin A
- Vitamin B$_6$
- Vitamin B$_{12}$
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- Vitamin D
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- Vitamin K

Biotin

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Summary

- Water-soluble biotin is an essential cofactor to enzymes in intermediary metabolism and a key regulator of gene expression. *(More information)*
- Both parenteral nutrition devoid of biotin and prolonged consumption of raw egg white have been associated with symptoms of frank biotin deficiency, including hair loss, dermatitis, skin rash, ataxia, seizures, and other neurologic dysfunctions. *(More information)*
- Biotinidase deficiency is a rare hereditary disorder that impairs biotin absorption and recycling, resulting in secondary biotin deficiency. *(More information)*
- The recommended adequate intake (AI) of biotin is set at 30 micrograms (μg)/day in adults. Biotin requirements are likely increased during pregnancy and breast-feeding. *(More information)*
- Animal studies have shown that biotin sufficiency is essential for normal fetal development. Yet, it is not known if marginal biotin deficiency during pregnancy increases the risk for congenital anomalies in humans. *(More information)*
- Biotin is used in the treatment of biotin-thiamin responsive basal ganglia disease, an inherited disorder of thiamin transport. *(More information)*
- Recent randomized controlled trials have not found high-dose biotin supplementation to be beneficial in the treatment of multiple sclerosis. Yet, results of animal studies and meta-analyses of human clinical trials are promising. *(More information)*
- Definitive evidence that establishes whether biotin supplementation improves glucose and lipid homeostasis in individuals with type 2 diabetes mellitus is currently lacking, but suggestive observations have been published. *(More information)*
- Biotin cannot be synthesized by mammalian cells and must be obtained from exogenous sources. Biotin is widely found in food, and good dietary sources include egg yolk, liver, whole-grain cereal, and some vegetables. *(More information)*
- Long-term anticonvulsant (anti-seizure) therapy may increase the dietary requirement for biotin because anticonvulsants can interfere with the intestinal absorption and renal re-absorption of biotin and likely also increase degradation of biotin to inactive metabolites. *(More information)*
- Use of high-dose biotin supplements can result in aberrant results of laboratory tests that utilize the very high affinity biotin-streptavidin (avidin) interaction. *(More information)*

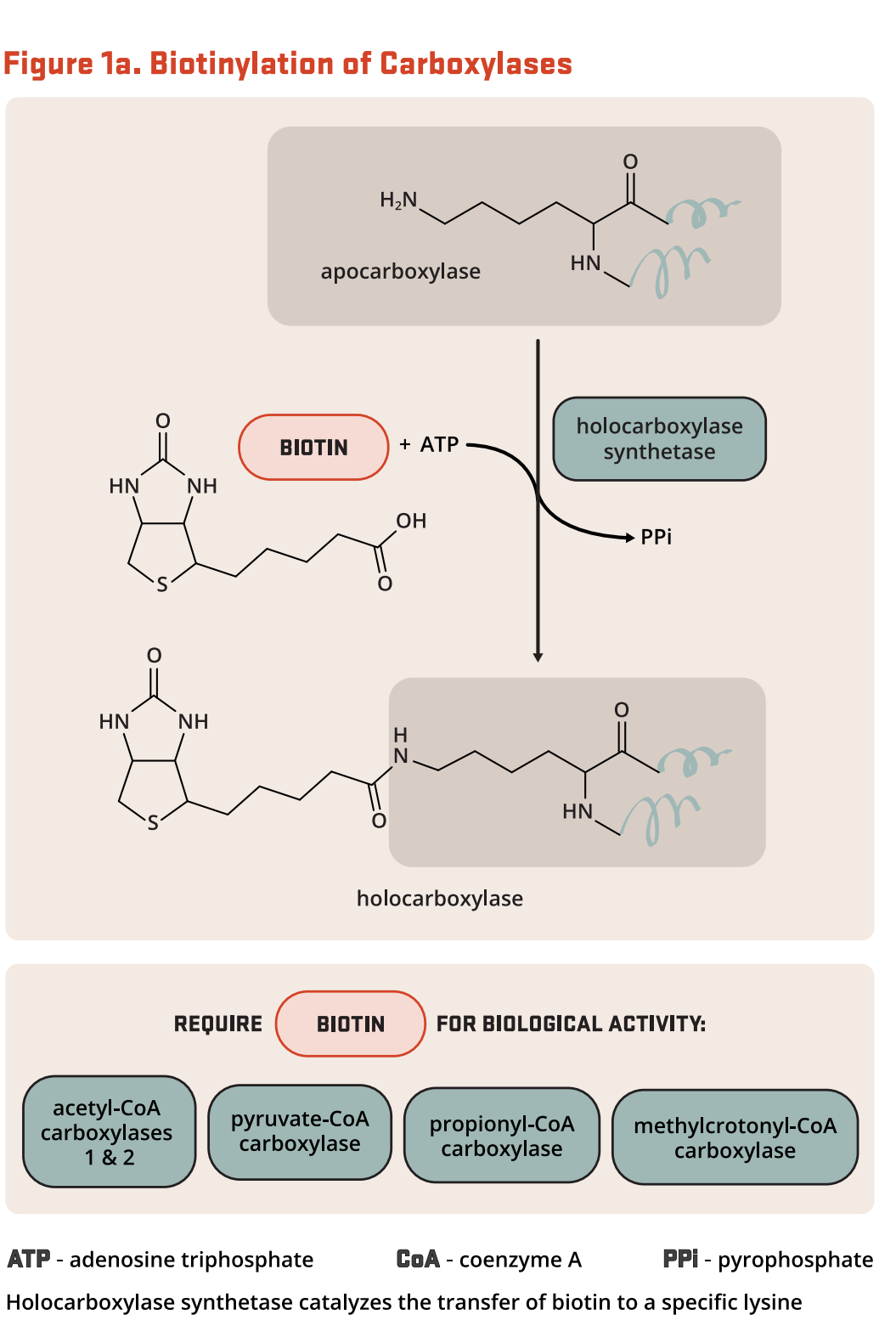
Biotin is a water-soluble vitamin that is generally classified as a B-complex vitamin. After its initial discovery in 1927, 40 years of additional research was required to unequivocally establish biotin as a vitamin (1). Biotin is required by all organisms but can be synthesized by some strains of bacteria, yeast, mold, algae, and some plant species (2).

Function

Biotinylation

Biotin functions as a covalently bound cofactor required for the biological activity of the five known mammalian biotin-dependent carboxylases (see below). Such non-protein cofactors are termed "prosthetic groups" and are common in water-soluble vitamins. The covalent attachment of biotin to the apocarboxylase (i.e., the carboxylase protein without the biotin prosthetic group and is catalytically inactive) is catalyzed by the enzyme, holocarboxylase synthetase (HCS). The term "biotinylation" refers to the covalent addition of biotin to any molecule, including the apocarboxylases and histones. HCS catalyzes the post-translational biotinylation of the epsilon amino group of a lysine residue at the active site of each apocarboxylase, converting the inactive apocarboxylase into a fully active holocarboxylase (**Figure 1a**). Particular lysine residues within the N-terminal tail of specific histone that help package DNA in eukaryotic nuclei can also be biotinylated (3). Biotinidase is the enzyme that catalyzes the release of biotin from biotinylated histones and from the peptide products of holocarboxylase breakdown (**Figure 1b**).

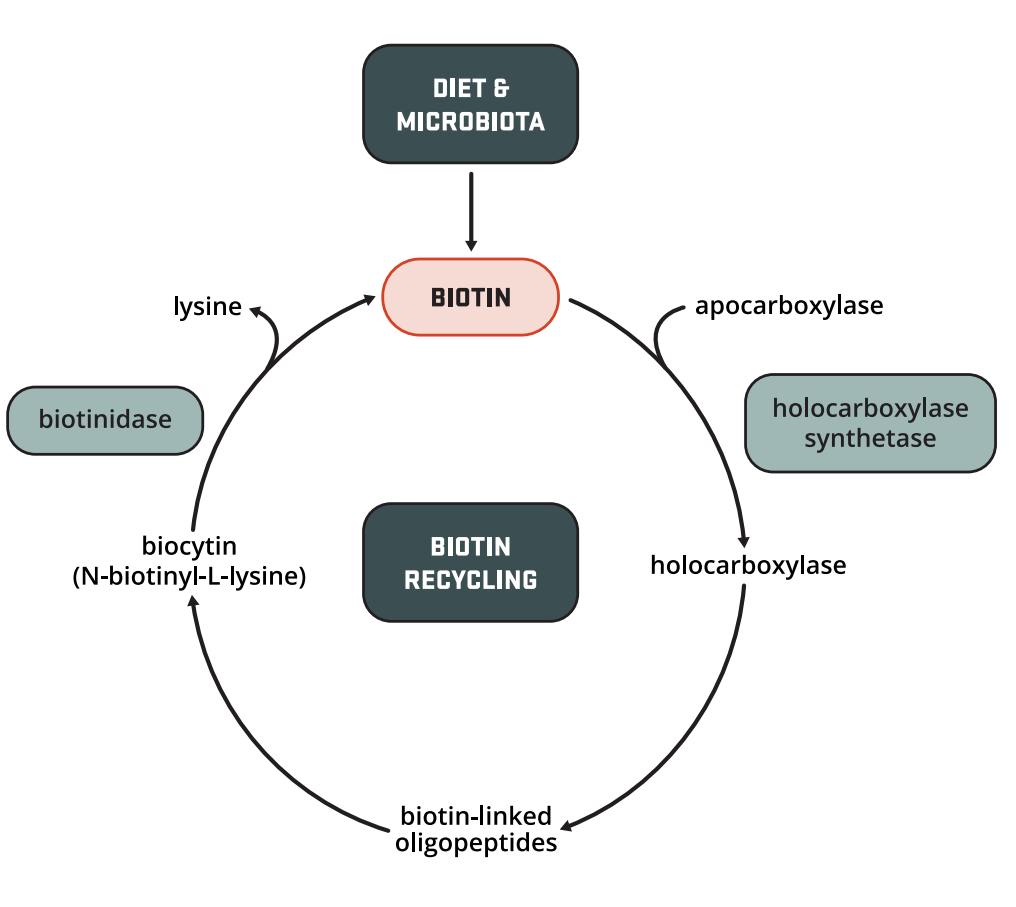
Figure 1a. Biotinylation of Carboxylases



H₂N
O
apocarboxylase
HN
BIOTIN
+ ATP
holocarboxylase synthetase
PPi
HN
NH
S
OH
H
N
holocarboxylase
REQUIRE BIOTIN FOR BIOLOGICAL ACTIVITY:
acetyl-CoA carboxylases 1 & 2
pyruvate-CoA carboxylase
propionyl-CoA carboxylase
methylcrotonyl-CoA carboxylase
ATP - adenosine triphosphate
CoA - coenzyme A
PPi - pyrophosphate

Holocarboxylase synthetase catalyzes the transfer of biotin to a specific lysine residue at the active site of apocarboxylase, converting the enzyme to a fully active holocarboxylase. Five mammalian carboxylases are known to require biotin for their biological activity: acetyl-CoA carboxylases 1 and 2, pyruvate-CoA carboxylase, propionyl-CoA carboxylase, and methylcrotonyl-CoA carboxylase.

Figure 1b. Biotin Recycling



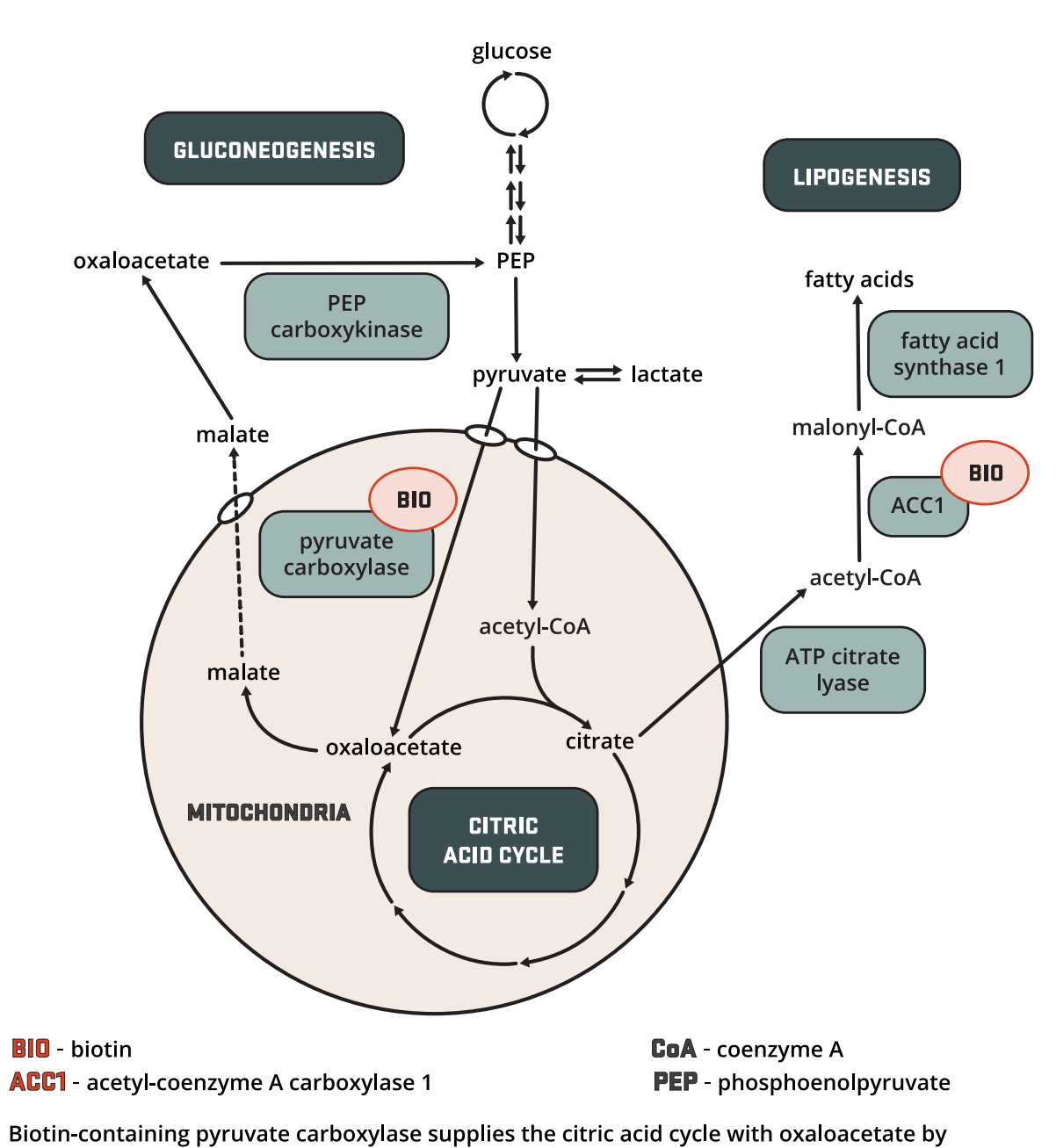
The biotinylation of apocarboxylase is catalyzed by holocarboxylase synthetase, while the enzyme biotinidase catalyzes the removal of biotin from the peptide products of carboxylase breakdown.

Enzyme cofactor

Five mammalian carboxylases catalyze essential metabolic reactions:

• Both **acetyl-Coenzyme A (CoA) carboxylase 1 (ACC1)** and **acetyl-CoA carboxylase 2 (ACC2)** catalyze the conversion of acetyl-CoA to malonyl-CoA using bicarbonate and ATP; however, the two enzymes have different roles in metabolism and different intracellular locations. ACC1 is located in the cytosol, and the malonyl CoA generated by ACC1 is a rate-limiting substrate for the synthesis of fatty acids (**Figure 2**). ACC1 is found in all tissues and is particularly active in lipogenic tissues (i.e., liver, white adipose tissue, and mammary gland), heart, and pancreatic islets. ACC2 is located on the outer mitochondrial membrane, and the malonyl CoA generated via ACC2 inhibits CPT1, an enzyme that regulates malonyl-CoA entry into the inner mitochondria, thereby regulating fatty acid oxidation (**Figure 3**). ACC2 is especially abundant in skeletal muscle and heart (4).

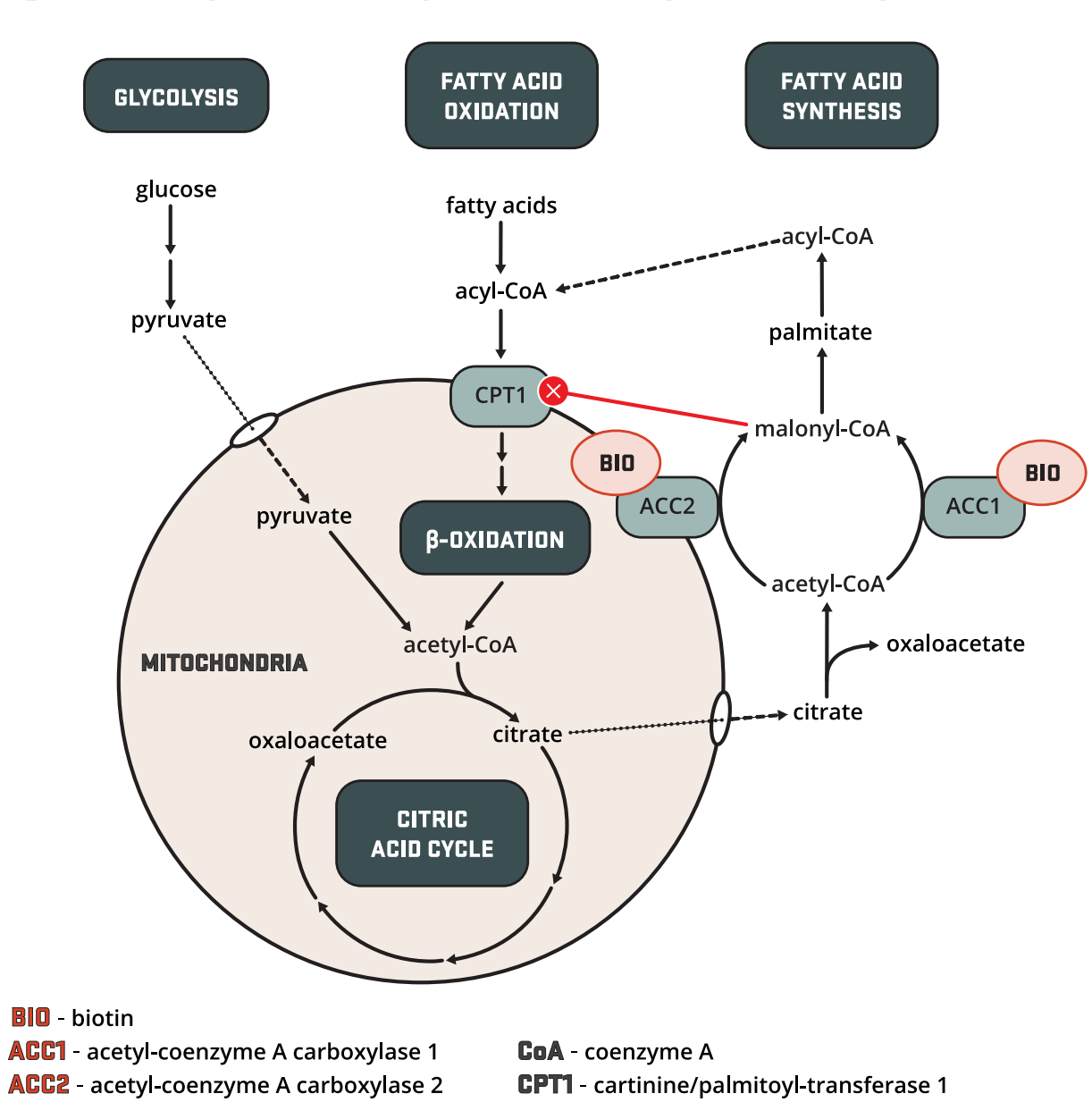
Figure 2. Pyruvate Carboxylase and Acetyl-CoA Carboxylase 1



Biotin-containing pyruvate carboxylase supplies the citric acid cycle with oxaloacetate by catalyzing the conversion of pyruvate to oxaloacetate using bicarbonate and ATP. In the liver, oxaloacetate can be used as a precursor for gluconeogenesis. It is first converted to phosphoenolpyruvate (PEP) by PEP carboxykinase and then to glucose via the reverse pathway of glycolysis. In the citric acid cycle, oxaloacetate can also be condensed with acetyl-CoA to produce citrate, which can be exported from the mitochondria. In the liver, adipose tissue, and skeletal muscle, citrate is cleaved to oxaloacetate and acetyl-CoA in the cytosol. Acetyl-CoA is converted to malonyl-CoA by another biotin-containing enzyme, acetyl-CoA carboxylase 1. Malonyl-CoA is then used by fatty acid synthase 1 to generate long-chain fatty acids.

• **Pyruvate carboxylase** is a critical enzyme in gluconeogenesis (the formation of glucose from sources other than carbohydrates, such as pyruvate, lactate, glycerol, and the glucogenic amino acids). Pyruvate carboxylase catalyzes the ATP-dependent incorporation of bicarbonate into pyruvate, producing oxaloacetate; hence, pyruvate carboxylase is anaplerotic for the citric acid cycle (**Figure 3**). Oxaloacetate can then be converted to phosphoenolpyruvate and eventually to glucose.

Figure 3. Acetyl-CoA Carboxylase 1 and Acetyl-CoA Carboxylase 2

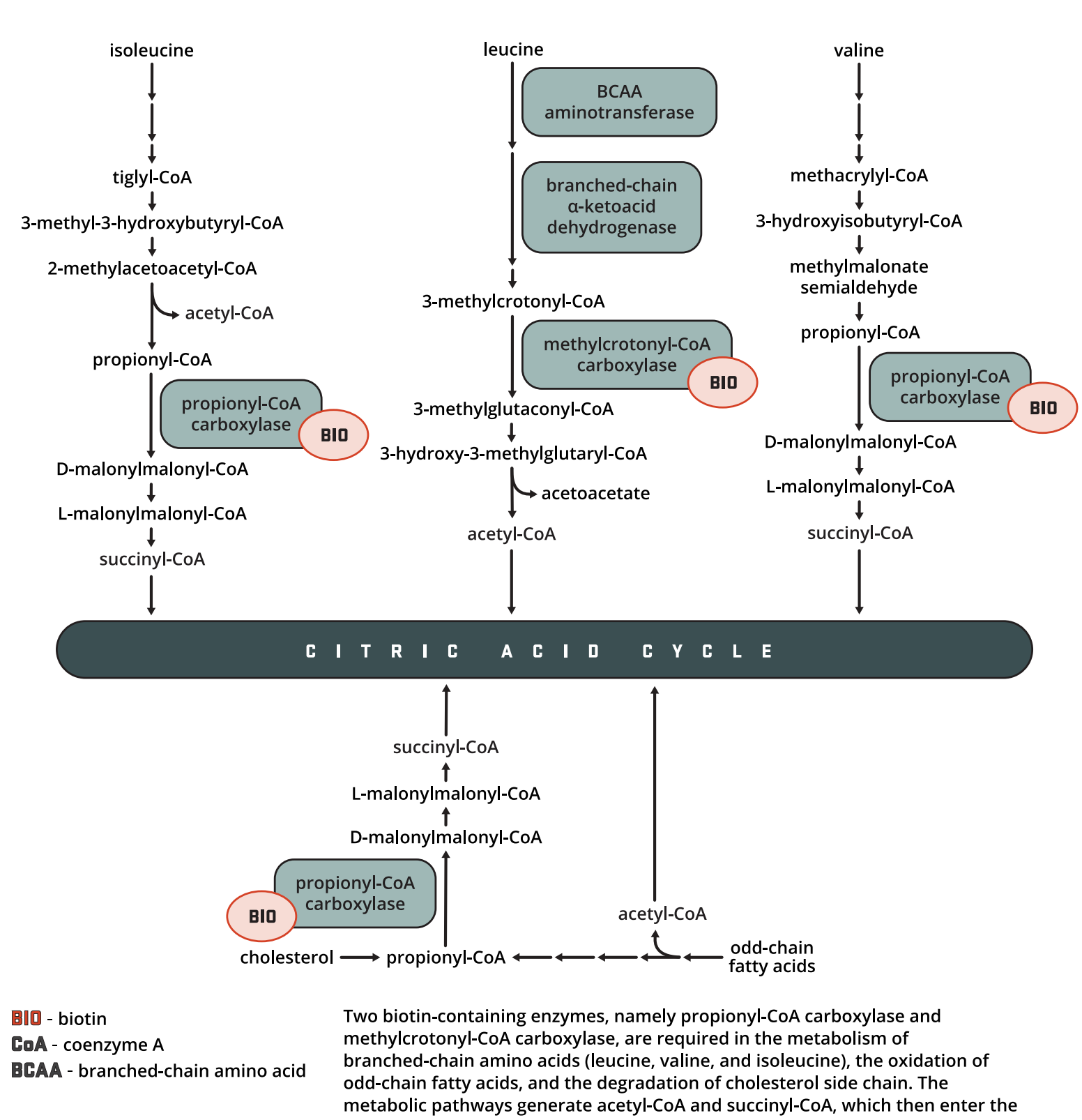


In the cytosol of liver cells, fatty acids are converted to acyl-CoA, and glucose undergoes glycolysis that produces pyruvate. Acyl-CoA is shuttled into the mitochondria via CPT1-mediated transport and undergoes β-oxidation that generates acetyl-CoA. In addition, pyruvate is converted to acetyl-CoA in the mitochondria, and acetyl-CoA is condensed with oxaloacetate to form citrate. The latter can be exported to the cytosol and cleaved to oxaloacetate and acetyl-CoA. Acetyl-CoA is used to generate malonyl-CoA in a reaction catalyzed by biotin-containing acetyl-CoA carboxylase 1 (ACC1) in the presence of ATP and bicarbonate. Malonyl-CoA is an essential substrate for the biosynthesis of fatty acids and subsequent triglycerides, phospholipids, and lipoproteins. Malonyl-CoA is also a regulator of fatty acid β-oxidation. Indeed, malonyl-CoA generated from acetyl-CoA by another biotin-containing enzyme, acetyl-CoA carboxylase 2 (ACC2), localized at the mitochondrial membrane, has been shown to downregulate fatty acid β-oxidation in the mitochondria by inhibiting CPT1.

• **Methylcrotonyl-CoA carboxylase** catalyzes an essential step in the catabolism of leucine, an essential branched-chain amino acid. This enzyme catalyzes the production of 3-methylglutaconyl-CoA from methylcrotonyl-CoA (**Figure 4a**).

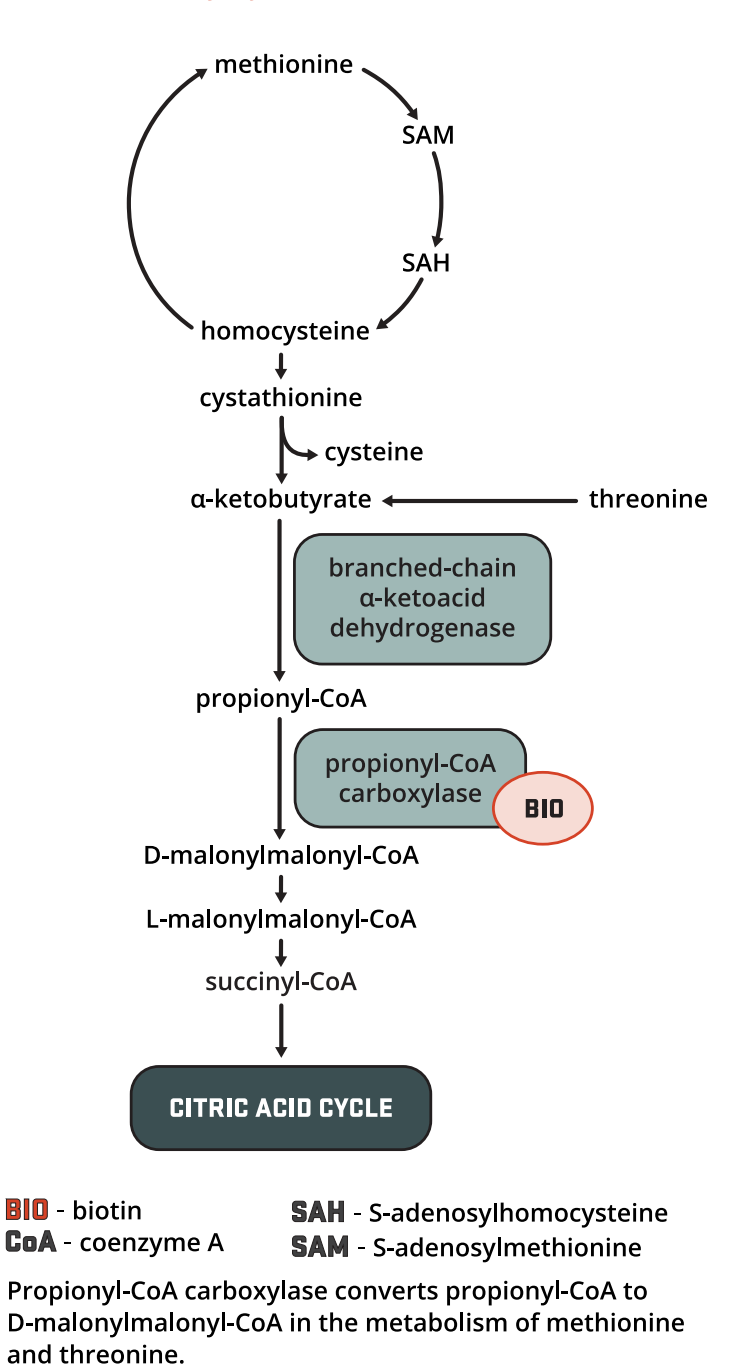
• **Propionyl-CoA carboxylase** produces D-malonylmalonyl-CoA from propionyl-CoA, a by-product in the β-oxidation of fatty acids with an odd number of carbon atoms (**Figure 4a**). The conversion of propionyl-CoA to D-malonylmalonyl-CoA is also required in the catabolic pathways of two branched-chain amino acids (isoleucine and valine) and the side chain of cholesterol (**Figure 4a**) and of the amino acids methionine and threonine (**Figure 4b**).

Figure 4a. Biotin-containing Carboxylases in the Metabolism of BCAAs, Odd-Chain Fatty Acids, and Cholesterol



Two biotin-containing enzymes, namely propionyl-CoA carboxylase and methylcrotonyl-CoA carboxylase, are required in the metabolism of branched-chain amino acids (leucine, valine, and isoleucine), the oxidation of odd-chain fatty acids, and the degradation of cholesterol side chain. The metabolic pathways generate acetyl-CoA and succinyl-CoA, which then enter the citric acid cycle.

Figure 4b. Biotin-containing Propionyl-CoA Carboxylase in the Metabolism of Methionine and Threonine



Propionyl-CoA carboxylase converts propionyl-CoA to D-malonylmalonyl-CoA in the metabolism of methionine and threonine.

Regulation of chromatin structure and gene expression

In eukaryotic nuclei, DNA is packaged into compact structures to form nucleosomes — fundamental units of chromatin. Each nucleosome is composed of 147 base pairs of DNA wrapped around eight histones (paired histones: H2A, H2B, H3, and H4). The H1 linker histone is located at the outer surface of each nucleosome and serves as an anchor to fix the DNA around the histone core. The compact packaging of chromatin must be relaxed for DNA replication and transcription. Chemical modifications of DNA and histones affect the folding of chromatin, increasing or reducing DNA accessibility to factors involved in replication and transcription. DNA methylation and a number of chemical modifications within the N-terminal tail of core histones modify their electric charge and structure, thereby changing chromatin conformation and transcriptional activity of genes.

The modifications of histone tails ("marks"), including acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, ADP-ribosylation, carbonylation, deimination, hydroxylation, and biotinylation, have various regulatory functions. Several sites of biotinylation have been identified in histones H2A, H3, and H4 (5). Amongst them, histone H4 biotinylation at lysine (K) 12 (noted H4K12bio) appears to be enriched in heterochromatin, a tightly condensed chromatin associated with repeat regions in (peri)centromeres and telomeres. H4 biotinylation appears to be enriched in transposable elements known as long terminal repeats (3). These biotinylation marks also co-localize with well-known gene repression marks like methylated lysine 9 in histone H3 (H3K9me) in transcriptionally competent chromatin (6). For example, H4K12bio can be found at the promoter of the gene *SLC5A6* that codes for the transporter mediating biotin uptake into cells, the human sodium-dependent multivitamin transporter (hSMVT). When biotin is abundant, HCS can biotinylate histones H4 in the *SLC5A6* promoter, which down regulates hSMVT synthesis and reduces biotin uptake. Conversely, in biotin-deficient cells, biotinylation marks in the *SLC5A6* promoter are removed increasing gene expression and enabling the synthesis of hSMVT and uptake of biotin (7).

Deficiency

Although clinically overt biotin deficiency is very rare, the human requirement for dietary biotin has been demonstrated in three different situations: prolonged intravenous feeding (parenteral) without biotin supplementation, infants fed an elemental formula devoid of biotin, and consumption of raw egg white for a prolonged period (many weeks to years) (8). Raw egg white contains avidin; this antimicrobial protein binds biotin with an affinity and specificity that is almost unique as a reversible binding. Because native avidin is resistant to mammalian and microbial digestion, avidin prevents biotin absorption. Cooking egg white denatures avidin, rendering it susceptible to digestion and therefore unable to block the absorption of dietary biotin (5).

Signs and symptoms of biotin deficiency

Signs of overt biotin deficiency include hair loss (alopecia) and a scaly red rash around the eyes, nose, mouth, and genital area. Neurologic symptoms in adults have included depression, lethargy, hallucinations, numbness and tingling of the extremities, ataxia, and seizures. The characteristic facial rash, together with unusual facial fat distribution, has been termed the "biotin deficient facies" by some investigators (1). Individuals with hereditary disorders of biotin metabolism (see Inborn metabolic disorders) that result in functional biotin deficiency often have similar physical findings, impaired immune system function, and increased susceptibility to bacterial and fungal infections (9, 10).

Risk factors for biotin deficiency

Aside from prolonged consumption of raw egg white or total intravenous nutritional support lacking biotin, other conditions may increase the risk of biotin depletion. Smoking has been associated with increased biotin catabolism (11). The rapidly dividing cells of the developing fetus require biotin for synthesis of essential carboxylases and for histone biotinylation; hence, the maternal biotin requirement is likely increased during pregnancy. Research suggests that a substantial number of women develop marginal or subclinical biotin deficiency during normal pregnancy (see also Disease Prevention) (8, 12, 13). Moreover, certain types of liver disease may decrease biotinidase activity and theoretically increase the requirement for biotin. For example, a study of 62 children with chronic liver disease and 27 healthy controls found serum biotinidase activity to be abnormally low in those with severely impaired liver function due to cirrhosis (14). However, this study did not provide evidence of biotin deficiency. Additionally, anticonvulsant medications used to prevent seizures in individuals with epilepsy increase the risk of biotin depletion (for more information on biotin and anticonvulsants, see Drug interactions).

Inborn metabolic disorders

Biotinidase deficiency

Biotinidase deficiency is an autosomal recessive inherited disorder that is often detected upon newborn screening for metabolic disorders, although late-onset forms have been recently described (15-17). Biotinidase deficiency leads to secondary biotin deficiency in several ways. Intestinal absorption is decreased because deficient biotinidase impairs release of biotin from dietary protein (18). Further, recycling of intracellular biotin bound to carboxylases and histones is also impaired, and urinary loss of biocytin (*N*-biotinyl-lysine) and biotin is increased (see **Figure 1** above) (5). Biotinidase deficiency responds to supplemental biotin. Oral supplementation with as much as 5 to 20 milligrams (mg) of biotin daily is sometimes required (19, 20), although smaller doses may be sufficient, especially later in childhood (reviewed in 20, 21). Prognosis is characteristically good when biotin therapy is introduced in infancy or early childhood and reliably continued for life (10).

Holocarboxylase synthetase deficiency

Holocarboxylase synthetase deficiency results in decreased formation of all holocarboxylases at physiological blood biotin concentrations; thus, high-dose biotin supplementation (10-80 mg of biotin daily) is required (10). Holocarboxylase synthetase deficiency responds to supplementation with pharmacologic doses of biotin in some cases but not others. The prognosis of holocarboxylase synthetase is usually, but not always, good if biotin therapy is introduced early (even antenatally) and continued for life (10, 22).

Biotin transport deficiency

There has been one case report of a child with biotin transport deficiency who responded to high-dose biotin supplementation (23). Of note, the presence of a defective human sodium-dependent multivitamin transporter (hSMVT) was ruled out as a cause of biotin transport deficiency.

Markers of biotin status

Four measures of marginal biotin deficiency have been validated as indicators of biotin status: and (1) reduced levels of holo-methylcrotonyl-CoA carboxylase and holo-propionyl-CoA carboxylase in lymphocytes, the most reliable indicators of biotin status (24); (2) reduced propionyl-CoA carboxylase activity in peripheral blood lymphocytes (5); (3) high urinary excretion of an organic acid, 3-hydroxyisovaleric acid, and its derivative, 3-hydroxyisovaleryl carnitine, both of which reflect decreased activity of biotin-dependent methylcrotonyl-CoA carboxylase; (4) reduced urinary excretion of biotin and some of its catabolites. These markers have been only validated in men and nonpregnant women, and they may not accurately reflect biotin status in pregnant or breast-feeding women (12, 25).

The Adequate Intake (AI)

Sufficient scientific evidence is lacking to estimate the dietary requirement for biotin; thus, no Recommended Dietary Allowance (RDA) for biotin has been established. Instead, the Food and Nutrition Board of the National Academy of Medicine set recommendations for an Adequate Intake (AI; **Table 1**). The AI for adults (30 μg/day) was extrapolated from the AI for infants exclusively fed human milk and probably overestimates the dietary requirement for biotin for most adults. Dietary intakes of generally healthy adults have been estimated to be 40 to 60 micrograms (μg) of biotin daily (1). The requirement for biotin in pregnancy may be increased (26).

Table 1. Adequate Intake (AI) for Biotin

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	5	5
Infants	7-12 months	6	6
Children	1-3 years	8	8
Children	4-8 years	12	12
Children	9-13 years	20	20
Adolescents	14-18 years	25	25
Adults	19 years and older	30	30
Pregnancy	all ages	-	30
Breast-feeding	all ages	-	35

Disease Prevention

Congenital anomalies

Current research indicates that at least one-third of women develop marginal biotin deficiency during pregnancy (8). Small observational studies in pregnant women have reported an abnormally high urinary excretion of 3-hydroxyisovaleric acid in both early and late pregnancy, suggesting decreased activity of biotin-dependent methylcrotonyl-CoA carboxylase (27, 28). In a randomized, single-blinded intervention study in 26 pregnant women, supplementation with 300 μg/day of biotin for two weeks limited the excretion of 3-hydroxyisovaleric acid compared to placebo, confirming that increased 3-hydroxyisovaleric acid excretion indeed reflected marginal biotin deficiency in pregnancy (29). A small cross-sectional study in 22 pregnant women reported an incidence of low lymphocyte propionyl-CoA carboxylase activity greater than 80% (13). Although these levels of biotin deficiency are not associated with overt signs of deficiency in pregnant women, such observations are sources of concern because subclinical biotin deficiency has been shown to cause cleft palate and limb hypoplasia in several animal species (reviewed in 13). In addition, biotin depletion has been found to suppress the expression of biotin-dependent carboxylases, remove biotin marks from histones, and decrease the proliferation in human embryonic palatal mesenchymal cells in culture (30). Impaired carboxylase activity may result in alterations in lipid metabolism, which have been linked to cleft palate and skeletal abnormalities in animals. Further, biotin deficiency leading to reduced histone biotinylation at specific genomic loci may increase genomic instability and result in chromosome anomalies and fetal malformations (13).

Analogous to pregnant women who are advised to consume supplemental folic acid prior to and during pregnancy to prevent neural tube defects (see Folate), it would also be prudent to ensure adequate biotin intake throughout pregnancy. The current AI for pregnant women is 30 μg/day of biotin, and no toxicity has ever been reported at this level of intake (see Safety).

Disease Treatment

Biotin-thiamin-responsive basal ganglia disease

Biotin-thiamin-responsive basal ganglia disease (also called biotin-responsive basal ganglia disease, thiamin transporter-2 deficiency, and thiamin metabolism dysfunction syndrome-2) is caused by an autosomal recessive mutation in the *SLC19A3* gene that codes for thiamin transporter-2 (THTR-2). The disease usually presents around 3 to 10 years of age (31), but an early infantile form of the disease exists with onset as early as one month of age (32). Clinical features include subacute encephalopathy (confusion, drowsiness, altered level of consciousness), ataxia, and seizures.

A retrospective study of 18 affected individuals from the same family or the same tribe in Saudi Arabia showed that biotin monotherapy (5-10 mg/kg/day) efficiently abolished the clinical manifestations of the disease, although one-third of the patients suffered from recurrent acute crises. Often associated with poor outcomes, acute crises were not observed after thiamin supplementation started (300-400 mg/day) and during a five-year follow-up period, early diagnosis and immediate treatment with biotin and thiamin led to positive outcomes (33). Although the specific mechanism for therapeutic effects of biotin in biotin-thiamin-responsive basal ganglia disease remains unknown, lifelong high-dose supplementation with a combination of biotin and thiamin is the recommended treatment (31). Early diagnosis and treatment is important to ensure a better prognosis (32, 34).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by progressive damage to the myelin sheath surrounding nerve fibers (axons) and neuronal loss in the brain and spinal cord of affected individuals in anatomic locations that vary widely among affected individuals producing variable signs and symptoms. The progression of neurologic disabilities in MS patients is often assessed by the Expanded Disability Status Scale (EDSS) with scores from 1 to 10, from minimal signs of motor dysfunction (score of 1) to death by MS (score of 10). ATP deficiency due to mitochondrial dysfunction and increased oxidative stress may be partly responsible for the progressive degeneration of neurons in MS (35). Given its role in energy production by intermediary metabolism and fatty acid oxidation and in fatty acid synthesis (required for myelin formation) (see Function), high-dose biotin supplementation it has been hypothesized that to exert beneficial effects that would limit or reverse MS-associated functional impairments (35).

The mechanism of action of high-dose biotin has been investigated in a genetic mouse model of chronic axon injury caused by oxidative damage and bioenergetic failure. High-dose biotin restored redox homeostasis, mitochondria biogenesis, and ATP levels, and reversed axonal death and locomotor impairment. Dysregulation of the transcriptional program for lipid synthesis and degradation in the spinal cord was also normalized, possibly as the result of hyperactivation of a nutrient/energy/redox sensor that controls protein synthesis restoring lipid homeostasis.

A nonrandomized, uncontrolled pilot study in 23 patients with progressive MS found high doses of biotin (100-600 mg/day) to be associated with sustained clinical improvements in five (out of five) patients with progressive visual loss and 16 (out of 18) patients with partial paralysis of the limbs after a mean three months following treatment onset (36). Additionally, a multicenter, randomized, placebo-controlled trial in 154 subjects with progressive MS reported that 13 out of 103 patients supplemented with high-dose, pharmaceutical-grade biotin (300 mg/day) for 12 months achieved MS-related disability reversal — assessed by improved EDSS or 25-foot walk time (37). In comparison, none of the 51 patients randomized to the placebo group showed significant clinical improvements (37). However, when this regimen of high-dose biotin supplementation was examined in a larger, international cohort of patients with progressive MS (326 patients receiving biotin and 316 patients receiving placebo), no benefits on EDSS or walk time were seen after 12 months (38). Moreover, a randomized, double-blind, placebo-controlled trial in 93 MS patients with chronic visual loss found that 300 mg/day of pharmaceutical-grade biotin for six months did not improve visual acuity, but an interesting trend favoring the biotin group was observed in the subgroup of patients with progressive optic neuritis (39). Moreover, a meta-analysis of three randomized controlled trials (2 on disability; 3 on adverse effects), involving 889 individuals diagnosed with MS (the preponderance of participants [830] had progressive MS while only 59 had remitting relapsing MS) was conducted (40). Pooling results of two trials found no benefit of high-dose biotin on MS-related disability, but there was significant heterogeneity between the trials. When the subgroup progressive MS was analyzed separately, a moderate certainty of evidence suggested a potential benefit in favor of high-dose biotin for the 25-foot minute walk time (40). On balance, studies remain inconclusive but promising.

Diabetes mellitus

Overt biotin deficiency has been shown to impair glucose utilization in mice (41) and cause fatal hypoglycemia in chickens. Overt biotin deficiency likely also causes abnormalities in glucose regulation in humans (see Function). One early human study reported lower serum biotin concentrations in 43 patients with type 2 diabetes mellitus compared to 64 control subjects without the disease; an inverse relationship between fasting blood glucose and biotin concentrations was observed as well (42). In a small, randomized, placebo-controlled intervention study in 28 patients with type 2 diabetes, daily supplementation with 9 milligrams (mg) of biotin for one month resulted in a 45% decrease in mean fasting blood glucose concentrations (42). Yet, another small study in 10 patients with type 2 diabetes and 7 controls without diabetes found no effect of biotin supplementation (15 mg/day) for 28 days on fasting blood glucose concentrations in either group (43). A more recent double-blind, placebo-controlled study by the same research group showed that the same biotin regimen lowered plasma triglyceride concentrations in patients with hypertriglyceridemia — independent of whether they had type 2 diabetes (44). In this study, biotin administration did not affect blood glucose concentrations in either patient group. Additionally, a few studies have shown that co-supplementation with biotin and chromium picolinate may be a beneficial adjunct therapy in patients with type 2 diabetes (45-48). For information on chromium supplementation as a monotherapy for type 2 diabetes, see the article on Chromium.

Potential mechanisms for the glucose and lipid effects have been suggested. As a cofactor of carboxylases required for fatty acid synthesis, biotin may increase the utilization of glucose for fat synthesis. Also, biotin stimulates glucokinase, a liver enzyme that increases synthesis of glycogen, the storage form of glucose. Biotin also triggers the secretion of insulin in the pancreas of rats and improves glucose homeostasis (50). Yet, reduced activity of ACC1 and ACC2 would be expected to reduce fatty acid synthesis and increase fatty acid oxidation, respectively. Hence, whether pharmacologic doses of biotin benefits the management of hyperglycemia in patients with impaired glucose tolerance remains unclear. Moreover, whether supplemental biotin lowers the risk of cardiovascular complications in patients with diabetes by reducing serum triglycerides and LDL-cholesterol remains to be proven (44-46).

Brittle fingernails (onychorrhexis)

The finding that biotin supplements were effective in treating hoof abnormalities in hoofed animals suggested that biotin might also be helpful in strengthening brittle fingernails in humans (50-52). Three uncontrolled trials examining the effects of biotin supplementation (2.5 mg/day for several months) in women with brittle fingernails have been published (53-55). In two of the trials, subjective evidence of clinical improvement was reported in 67%-91% of the participants available for follow-up at the end of the treatment period (53, 54). One trial that used scanning electron microscopy to assess fingernail brittleness reported less fingernail splitting and a 25% increase in the thickness of the nail plate in patients supplemented with biotin for 6 to 15 months (55). Biotin supplementation (5 mg/day) was also found to be effective in controlling unruly hair and splitting nails in two toddlers with inherited uncombable hair syndrome (56). Although preliminary evidence suggests that supplemental biotin may help strengthen fragile nails (reviewed in 57), larger placebo-controlled trials are needed to assess the efficacy of high-dose biotin supplementation for the treatment of brittle fingernails.

Hair loss (alopecia)

Biotin administration has been associated with alopecia reversal in children treated with the anticonvulsant valproic acid (see Drug interactions), as well as with hair regrowth or normal hair growth in some children with inborn errors of biotin metabolism or other genetic disorders (i.e., uncombable hair syndrome) (reviewed in 58). Yet, while hair loss is a symptom of severe biotin deficiency (see Deficiency), there are no published scientific studies that support the claim that high-dose biotin supplements are effective in preventing or treating hair loss in men or women (59, 60). Randomized, placebo-controlled trials in healthy individuals would be needed to evaluate this claim.

Sources

Food sources

Biotin is found in many foods, either as the free (i.e., unbound) form that is directly taken up by enterocytes or as biotin bound to dietary proteins. Egg yolk, liver, and yeast are rich sources of biotin. Estimates of average daily intakes of biotin from small studies ranged between 40 and 60 micrograms (μg) per day in adults (1). However, US national nutritional surveys have not yet been able to estimate biotin intake due to the scarcity and unreliability of data regarding biotin content of food. Food composition tables for biotin are incomplete such that dietary intakes cannot be reliably estimated in humans. A study by Staggs et al. (61) employed a high-performance liquid chromatography method rather than bioassays (62) and reported relatively different biotin content for some selected foods. **Table 2** lists some food sources of biotin, along with their content in μg.

Table 2. Some Food Sources of Biotin (61, 62)

Food	Serving	Biotin (μg)
Yeast	1 packet (7 grams)	1.4-14
Bread, whole-wheat	1 slice	0.02-6
Egg, cooked	1 large	13-25
Cheese, cheddar	1 ounce	0.4-2
Liver, cooked	3 ounces*	27-35
Pork, cooked	3 ounces*	2-4
Salmon, cooked	3 ounces*	4-5
Avocado	1 whole	2-6
Raspberries	1 cup	0.2-2
Cauliflower, raw	1 cup	0.2-4
*A three-ounce serving of meat is about the size of a deck of cards.		

Bacterial synthesis

A majority of bacteria that normally colonize the small and large intestine (colon) synthesize biotin (63). Whether the biotin is released and absorbed by humans in meaningful amounts remains unknown. The uptake of free biotin into intestinal cells via the human sodium-dependent multivitamin transporter (hSMVT) has been identified in cultured cells derived from the lining of the small intestine and colon (64), suggesting that humans may be able to absorb biotin produced by enteric bacteria — a phenomenon documented in swine.

Supplements

Biotin is available as a single-nutrient supplement in various doses (many containing 5,000 μg [5 mg] of biotin) and is often included in B-complex and multivitamin-mineral supplements. Several multivitamin supplements contain 30 μg of biotin, although the amount varies by product (65).

Safety

Toxicity

Biotin is not known to be toxic. In people without disorders of biotin metabolism, doses of up to 5 mg/day (5,000 μg) for two years were not associated with adverse effects (66). Oral biotin supplementation has been well tolerated in doses up to 200 mg/day (nearly 7,000 times the AI) in people with hereditary disorders of biotin metabolism (1). Daily supplementation with a highly concentrated formulation of biotin (100-600 mg) for several months was also found to be well tolerated in individuals with progressive multiple sclerosis (36, 67). However, there is one case report of life-threatening eosinophilic pleuropericardial effusion in an elderly woman who took a combination of 10 mg/day of biotin and 300 mg/day of pantothenic acid (vitamin B$_5$) for two months (68). Because reports of adverse events were lacking when the Dietary Reference Intakes (DRIs) for biotin were established in 1998, the Food and Nutrition Board did not establish a tolerable upper intake level (UL) for biotin (1).

Nutrient interactions

Large doses of pantothenic acid (vitamin B$_5$) have the potential to compete with biotin for intestinal and cellular uptake by the human sodium-dependent multivitamin transporter (hSMVT) (69, 70). Biotin also shares the hSMVT with lipoic acid (71). Pharmacologic (very high) doses of lipoic acid have been found to decrease the activity of biotin-dependent carboxylases in rats, but such an effect has not been demonstrated in humans (72).

Drug interactions

Individuals on long-term anticonvulsant (anti-seizure) therapy reportedly have reduced blood biotin concentrations, as well as an increased urinary excretion of organic acids (e.g., 3-hydroxyisovaleric acid) that indicate decreased carboxylase activity (see Markers of biotin status) (5). Potential mechanisms of biotin depletion by the anticonvulsants, primidone (Mysoline), phenytoin (Dilantin, Phenytek), and carbamazepine (Carbatrol, Epitol, Equetro, Tegretol), include inhibition of biotin intestinal absorption and renal reabsorption, as well as increased biotin catabolism (73). Use of the anticonvulsant valproic acid in children has resulted in hair loss reversed by biotin supplementation (74-77). Long-term treatment with antibacterial sulfonamide (sulfa) drugs or other antibiotics may decrease bacterial synthesis of biotin. Yet, given that the extent to which bacterial synthesis contributes to biotin intake in humans is not known, effects of antimicrobial drugs on biotin nutritional status remain uncertain (73).

Interference with lab assays

In 2017, the US Food and Drug Administration (FDA) released a safety communication regarding high-dose biotin supplementation and its potential interference with streptavidin (avidin)-biotin immunoassays, including assays of thyroid hormones, reproductive hormones, and the cardiac protein, troponin. Such interference can cause aberrant results — either falsely high or falsely low depending on the method of the particular assay — and potential misdiagnosis of disease (78-81). An updated FDA communication in 2019 focused on biotin interference in certain lab assays of troponin that have not addressed the concern of falsely low blood concentrations (82). Troponin in blood is a marker of cardiac damage and often used in the clinical diagnosis of a myocardial infarction (heart attack). When blood work is planned, patients should routinely inform their health care provider concerning supplementation of biotin at doses substantially greater than those in usual diets or in routine daily multivitamins.

Linus Pauling Institute Recommendation

Little is known regarding the amount of dietary biotin required to promote optimal health or prevent chronic disease. The Linus Pauling Institute supports the recommendation made by the National Academy of Medicine, which is 30 micrograms (μg) of biotin per day for adults. A varied diet should provide enough biotin for most people. However, following the Linus Pauling Institute recommendation to take a daily multivitamin-mineral supplement will generally provide an intake of at least 30 μg/day of biotin.

Older adults (>50 years)

Presently, there is no indication that older adults have an increased requirement for biotin. If dietary biotin intake is not sufficient, a daily multivitamin-mineral supplement will generally provide an intake of at least 30 μg of biotin per day.

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Folate

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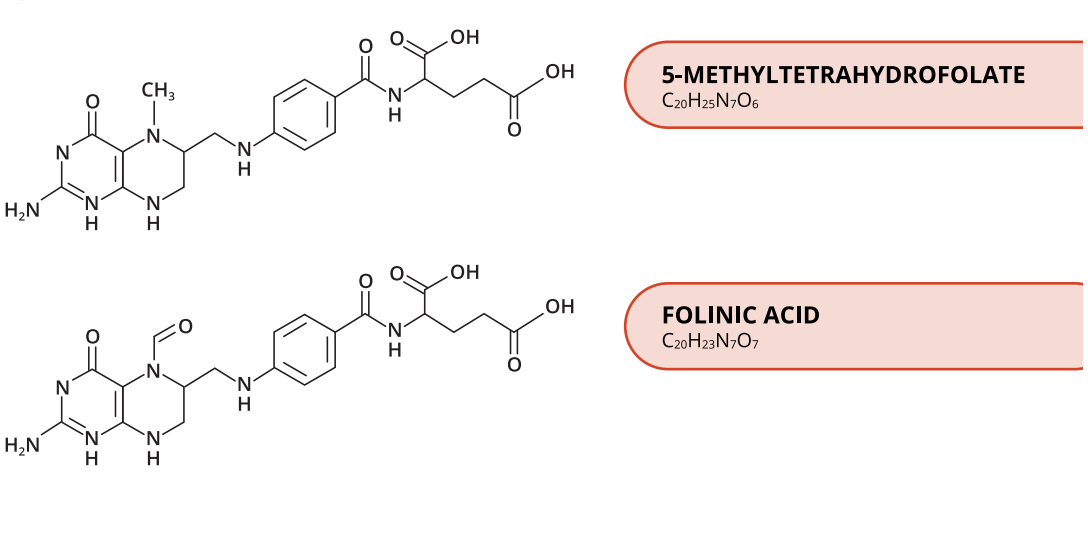
Summary

- Folate is a generic term referring to both natural folates in food and folic acid, the synthetic form used in supplements and fortified food. Folate is critical in the metabolism of nucleic acid precursors and several amino acids, as well as in methylation reactions. *(More information)*
- Severe deficiency in either folate or vitamin B_{12} can lead to megaloblastic anemia, which causes fatigue, weakness, and shortness of breath. Improper treatment of vitamin B_{12}-dependent megaloblastic anemia with high dose supplemental folic acid can potentially delay the diagnosis of vitamin B_{12} deficiency and thus leave the individual at risk of developing irreversible brain damage. *(More information)*
- Folate status is influenced by the presence of genetic variations in folate metabolism, particularly those found in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene. *(More information)*
- Inadequate folate status during early pregnancy increases the risk of congenital anomalies. The introduction of mandatory folic acid fortification of refined grain products in the US in 1998 has reduced the prevalence of neural tube defects (NTDs) in newborns. Yet, folate status is considered inadequate in a majority of women of childbearing age worldwide. Moreover, genetic factors might modify the risk of NTDs by increasing the susceptibility to folate deficiency during pregnancy. Several studies are currently investigating the role of folic acid supplementation in the prevention of congenital anomalies other than NTDs. *(More information)*
- Folate deficiency and elevated concentrations of homocysteine in the blood are associated with increased risk of cardiovascular disease (CVD). Although folic acid supplementation has been proven effective to control circulating homocysteine concentrations, the effect of homocysteine lowering on the incidence of CVD is still debated. *(More information)*
- Low folate status has been linked to increased cancer risk. However, intervention trials with high doses of folic acid have not generally shown any benefit on cancer incidence. *(More information)*
- Prospective cohort studies have reported an inverse association between folate status and colorectal cancer (CRC) risk, especially among men. The relationship between folate status and cancer risk is however complex and requires further research. *(More information)*
- Folate is essential for brain development and function. Low folate status and/or high homocysteine concentrations are associated with cognitive dysfunction in aging (from mild impairments to dementia). Whether supplemental B-vitamins, including folic acid, will have long-term benefits in maintaining cognitive health is not yet known. *(More information)*
- Several autosomal recessive disorders affecting folate transport and metabolism can be treated with high doses of folinic acid, a folate derivative. *(More information)*

Folate is a water-soluble B-vitamin, which is also known as vitamin B_9 or folacin. Naturally occurring folates exist in many chemical forms; folates are found in food, as well as in metabolically active forms in the human body. Folic acid is the major synthetic form found in fortified foods and vitamin supplements. Other synthetic forms include folinic acid (**Figure 1**) and levomefolic acid. Folic acid has no biological activity unless converted into folates (1). In the following discussion, forms found in food or the body are referred to as "folates," while the form found in supplements or fortified food is referred to as "folic acid."

Figure 1. Chemical Structures

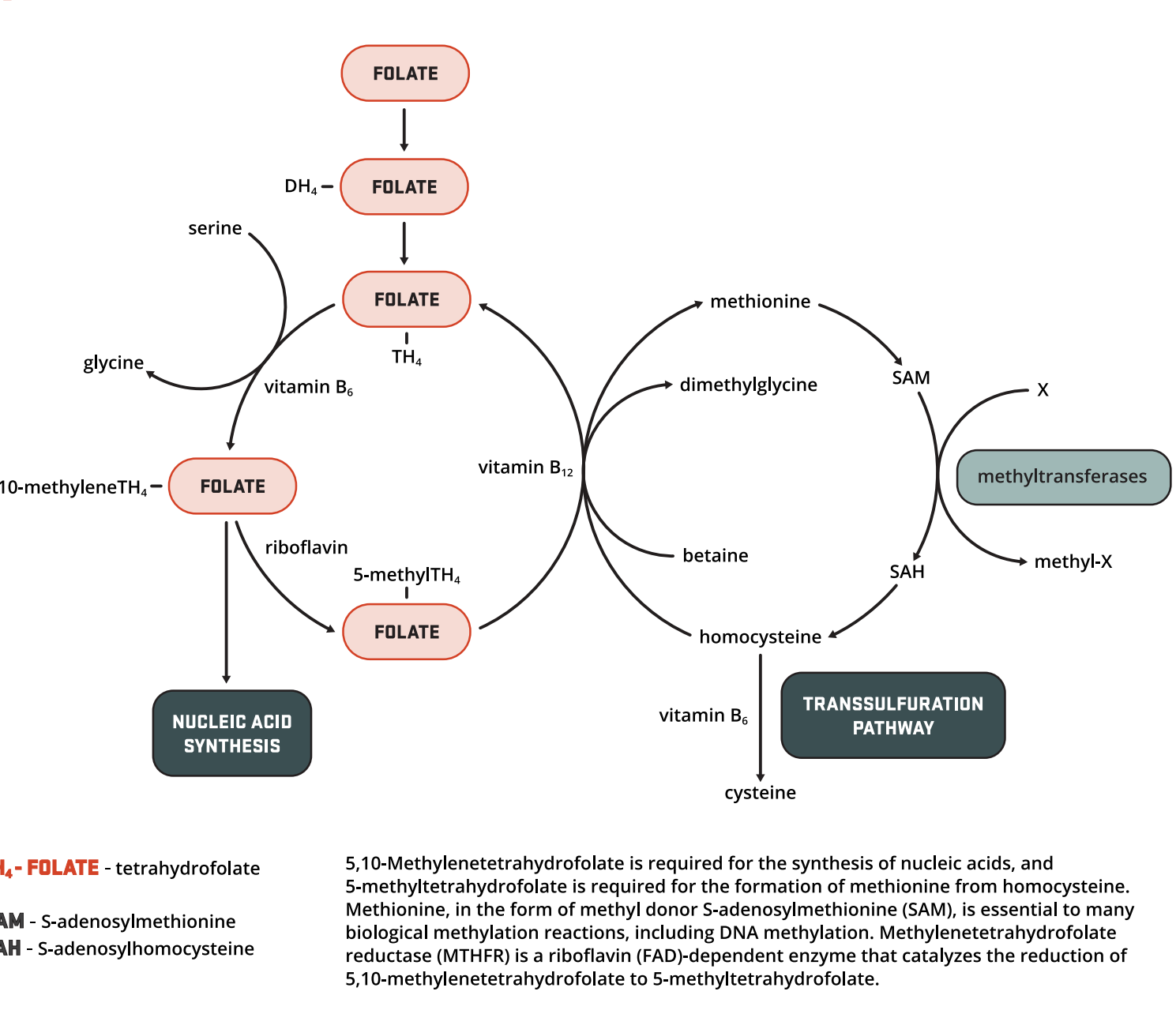


Function

One-carbon metabolism

The only function of folate coenzymes in the body appears to be in mediating the transfer of one-carbon units (2). Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids (**Figure 2**) (3).

Figure 2. Overview of One-carbon Metabolism



5,10-Methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.

Nucleic acid metabolism

Folate coenzymes play a vital role in DNA metabolism through two different pathways. (1) The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes. (2) A folate coenzyme is required for the synthesis of methionine from homocysteine, and methionine is required for the synthesis of S-adenosylmethionine (SAM). SAM is a methyl group (one-carbon unit) donor used in most biological methylation reactions, including the methylation of a number of sites within DNA, RNA, proteins, and phospholipids. The methylation of DNA plays a role in controlling gene expression and is critical during cell differentiation. Aberrations in DNA methylation have been linked to the development of cancer (see Cancer).

Amino acid metabolism

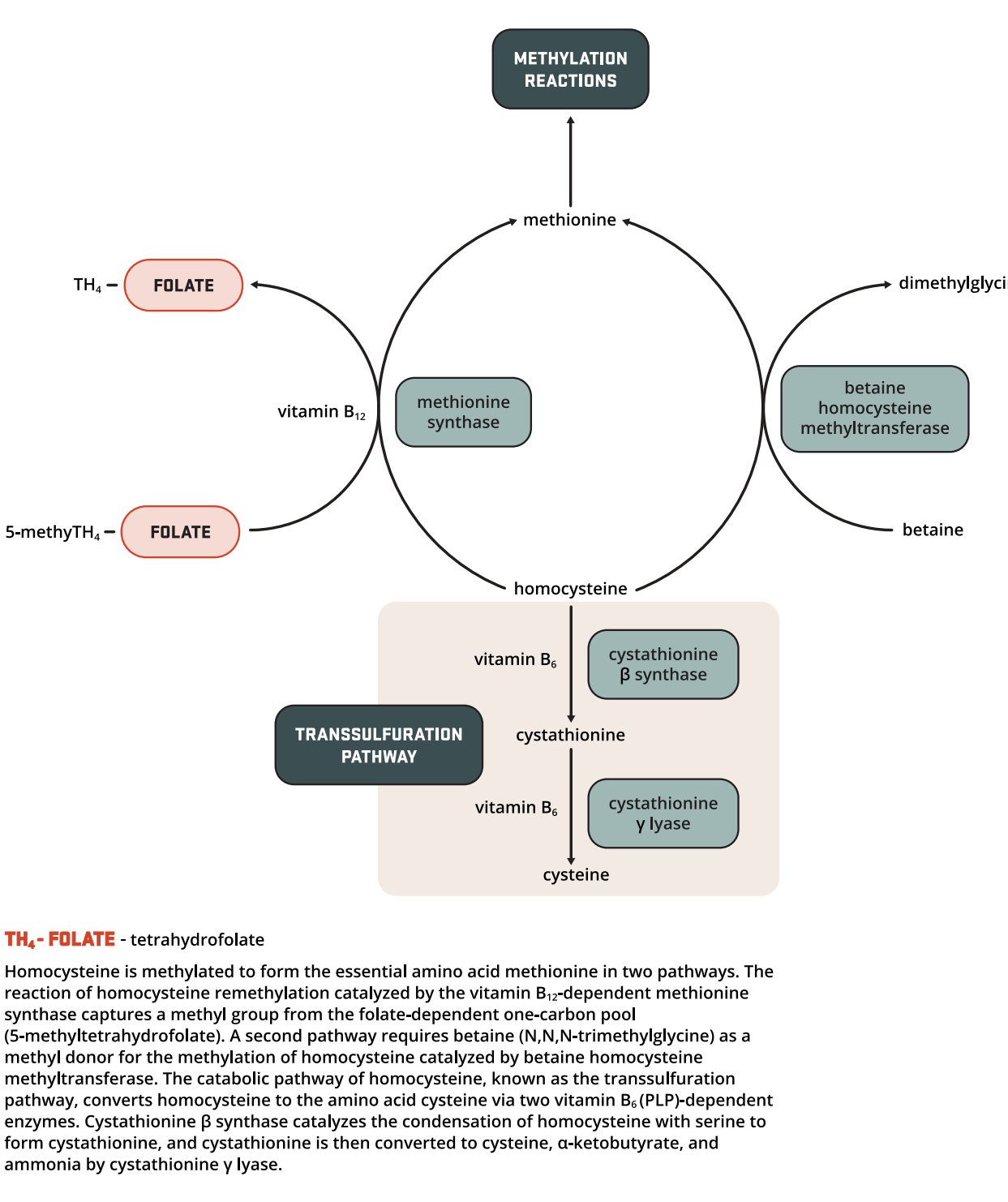
Folate coenzymes are required for the metabolism of several important amino acids, namely methionine, cysteine, serine, glycine, and histidine. The synthesis of methionine from homocysteine is catalyzed by methionine synthase, an enzyme that requires not only folate (as 5-methyltetrahydrofolate) but also vitamin B_{12}. Thus, folate (and/or vitamin B_{12}) deficiency can result in decreased synthesis of methionine and an accumulation of homocysteine. Elevated blood concentrations of homocysteine have been considered for many years to be a risk factor for some chronic diseases, including cardiovascular disease and dementia (see Disease Prevention).

Nutrient interactions

Vitamin B_{12} and vitamin B_6

The metabolism of homocysteine, an intermediate in the metabolism of sulfur-containing amino acids, provides an example of the interrelationships among nutrients necessary for optimal physiological function and health. Healthy individuals utilize two different pathways to metabolize homocysteine (**Figure 3**). One pathway (methionine synthase) synthesizes methionine from homocysteine and is dependent on both folate and vitamin B_{12} as cofactors. The other pathway converts homocysteine to another amino acid, cysteine, and requires two vitamin B_6-dependent enzymes. Thus, the concentration of homocysteine in the blood is regulated by three B-vitamins: folate, vitamin B_{12}, and vitamin B_6 (4). In some individuals, riboflavin (vitamin B_2) is also involved in the regulation of homocysteine concentrations (see the article on Riboflavin).

Figure 3. Homocysteine Metabolism



Homocysteine is methylated to form the essential amino acid methionine in two pathways. The reaction of homocysteine remethylation catalyzed by the vitamin B_{12}-dependent methionine synthase captures a methyl group from the folate-dependent one-carbon pool (5-methyltetrahydrofolate). A second pathway requires betaine (N,N,N-trimethylglycine) as a methyl donor for the methylation of homocysteine catalyzed by betaine homocysteine methyltransferase. The catabolic pathway of homocysteine, known as the transsulfuration pathway, converts homocysteine to the amino acid cysteine via two vitamin B_6 (PLP)-dependent enzymes. Cystathionine β synthase catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionine is then converted to cysteine, α-ketobutyrate, and ammonia by cystathionine γ lyase.

Riboflavin

Although less well recognized, folate has an important metabolic interaction with riboflavin. Riboflavin is a precursor of flavin adenine dinucleotide (FAD), a coenzyme required for the activity of the folate-metabolizing enzyme, 5,10-methylenetetrahydrofolate reductase (MTHFR). FAD-dependent MTHFR in turn catalyzes the reaction that generates 5-methyltetrahydrofolate (see **Figure 2** above). This active form of folate is required to form methionine from homocysteine. Along with other B-vitamins, higher riboflavin intakes have been associated with decreased plasma homocysteine concentrations (5). The effects of riboflavin on folate metabolism appear to be greatest in individuals homozygous for the common c.677C>T polymorphism (i.e., TT genotype) in the *MTHFR* gene (see Genetic variation in folate requirements) (6). These individuals (about 10% of adults worldwide) typically present with low folate status, along with elevated homocysteine concentrations, particularly when folate and/or riboflavin intake is suboptimal. The elevated homocysteine concentration in these individuals, however, is highly responsive to lowering with riboflavin supplementation, confirming the importance of the riboflavin-*MTHFR* interaction (7).

Vitamin C

Vitamin C may limit degradation of natural folate coenzymes and supplemental folic acid in the stomach and thus improve folate bioavailability. A cross-over trial in nine healthy men found that oral co-administration of 5-methyltetrahydrofolic acid (343 μg) and vitamin C (289 mg or 974 mg) was associated with higher concentrations of serum folate compared to 5-methyltetrahydrofolic acid alone (8). Moreover, a recent study suggested that several genetic variations of folate metabolism might influence the effect of vitamin C on folate metabolism (9).

Bioavailability

Dietary folates exist predominantly in the polyglutamyl form (containing several glutamate residues), whereas folic acid—the synthetic vitamin form—is a monoglutamate, containing just one glutamate moiety. In addition, natural folates are reduced molecules, whereas folic acid is fully oxidized. These chemical differences have major implications for the bioavailability of the vitamin such that folic acid is considerably more bioavailable than naturally occurring food folates at equivalent intake levels.

The intestinal absorption of dietary folates is a two-step process that involves the hydrolysis of folate polyglutamates to the corresponding monoglutamyl derivatives, followed by their transport into intestinal cells. There, folic acid is converted into a naturally occurring folate, namely 5-methyltetrahydrofolate, which is the major circulating form of folate in the human body (see **Figure 1** above).

The bioavailability of naturally occurring folates is inherently limited and variable. There is much variability in the ease with which folates are released from different food matrices, and the polyglutamyl "tail" is removed (de-conjugation) before uptake by intestinal cells. Also, other dietary constituents can contribute to instability of labile folates during the processes of digestion. As a result, naturally occurring folates show incomplete bioavailability compared with folic acid. The bioavailability of folic acid, in contrast, is assumed to be 100% when ingested as a supplement, while folic acid in fortified food is estimated to have about 85% the bioavailability of supplemental folic acid.

Of note, folate recommendations in the US and certain other countries are now expressed as Dietary Folate Equivalents (DFEs), a calculation that was devised to take into account the greater bioavailability of folic acid compared to naturally occurring dietary folates (see The Recommended Dietary Allowance).

Transport

Folate and its coenzymes require transporters to cross cell membranes. Folate transporters include the reduced folate carrier (RFC), the proton-coupled folate transporter (PCFT), and the folate receptor proteins, FRα and FRβ. Folate homeostasis is supported by the ubiquitous distribution of folate transporters, although abundance and importance vary among tissues (10). PCFT plays a major role in folate intestinal transport since mutations affecting the gene encoding PCFT cause hereditary folate malabsorption. Defective PCFT also leads to impaired folate transport into the brain (see Disease Treatment). FRα and RFC are also critical for folate transport across the blood-brain barrier when extracellular folate is either low or high, respectively. Folate is essential for the proper development of the embryo and the fetus. The placenta is known to concentrate folate to the fetal circulation, leading to higher folate concentrations in the fetus compared to those found in the pregnant woman. All three types of receptors have been associated with folate transport across the placenta during pregnancy (11).

Deficiency

Causes

Folate deficiency is most often caused by a dietary insufficiency; however, folate deficiency can also occur in a number of other situations. For example, chronic and heavy alcohol consumption is associated with diminished absorption of folate (in addition to low dietary intake), which can lead to folate deficiency (12). Smoking is also associated with low folate status. In one study, folate concentrations in blood were about 15% lower in smokers compared to nonsmokers (13). Additionally, impaired folate transport to the fetus has been described in pregnant women who either smoked or abused alcohol during their pregnancy (14, 15).

Pregnancy is a time when the folate requirement is greatly increased to sustain the demand for rapid cell replication and growth of fetal, placental, and maternal tissue. Conditions such as cancer or inflammation can also result in increased rates of cell division and metabolism, causing an increase in the body's demand for folate (16). Moreover, folate deficiency can result from some malabsorptive conditions, including inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and celiac disease (17). Several medications may also contribute to folate deficiency (see Drug interactions). Finally, a number of genetic diseases affecting folate absorption, transport, or metabolism can cause folate deficiency or impede its metabolic functions (see Disease Treatment).

Symptoms

Clinical folate deficiency leads to megaloblastic anemia, which is reversible with folic acid treatment. Rapidly dividing cells like those derived from bone marrow are most vulnerable to the effects of folate deficiency since DNA synthesis and cell division are dependent on folate coenzymes. When folate supply to the rapidly dividing cells of the bone marrow is inadequate, blood cell division is reduced, resulting in fewer but larger red blood cells. This type of anemia is called megaloblastic or macrocytic anemia, referring to the enlarged, immature red blood cells. Neutrophils, a type of white blood cell, become hypersegmented, a change that can be found by examining a blood sample microscopically. Because normal red blood cells have a lifetime in the circulation of approximately four months, it can take months for folate-deficient individuals to develop the characteristic megaloblastic anemia. Progression of such an anemia leads to a decreased oxygen carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath (1). It is important to point out that megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B_{12} deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia (see Toxicity).

Individuals in the early stages of folate deficiency may not show obvious symptoms, but blood concentrations of homocysteine may increase (see Disease Prevention). Yet, the concentration of circulating homocysteine is not a specific indicator of folate status, as elevated homocysteine can be the result of vitamin B_{12} and other B-vitamin deficiencies, lifestyle factors, and renal insufficiency. Subclinical deficiency is typically detected by measurement of folate concentrations in serum/plasma or in red blood cells.

The Recommended Dietary Allowance (RDA)

Determination of the RDA

Traditionally, the dietary folate requirement was defined as the amount needed to prevent a deficiency severe enough to cause symptoms like anemia. The most recent RDA (1998; **Table 1**) was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, as judged by the absence of abnormal hematological indicators. Red cell folate has been shown to correlate with liver folate stores and is used as an indicator of long-term folate status. Plasma folate reflects recent folate intake and is not a reliable biomarker for folate status. Maintenance of normal blood homocysteine concentrations, an indicator of one-carbon metabolism, was considered only as an ancillary indicator of adequate folate intake.

Because pregnancy is associated with a significant increase in cell division and other metabolic processes that require folate coenzymes, the RDA for pregnant women is considerably higher than for women who are not pregnant (3). However, the prevention of neural tube defects (NTDs) was not considered when setting the RDA for pregnant women. Rather, reducing the risk of NTDs was considered in a separate recommendation for women capable of becoming pregnant (see Disease Prevention), because the crucial events in the development of the neural tube occur before many women are aware that they are pregnant (18).

Dietary Folate Equivalents (DFEs)

When the Food and Nutrition Board of the US Institute of Medicine set the new dietary recommendation for folate, they introduced a new unit, the Dietary Folate Equivalent (DFE) (1). Use of the DFE reflects the higher bioavailability of synthetic folic acid found in supplements and fortified food compared to that of naturally occurring food folates (18).

- 1 microgram (μg) of food folate provides 1 μg of DFEs
- 1 μg of folic acid taken with meals or as fortified food provides 1.7 μg of DFEs
- 1 μg of folic acid (supplement) taken on an empty stomach provides 2 μg of DFEs

For example, a serving of food containing 60 μg of folate would provide 60 μg of DFEs, while a serving of pasta fortified with 60 μg of folic acid would provide 1.7 x 60 = 102 μg of DFEs due to the higher bioavailability of folic acid. A folic acid supplement of 400 μg taken on an empty stomach would provide 800 μg of DFEs. It should be noted that DFEs were determined in studies with adults and whether folic acid in infant formula is more bioavailable than folates in mother's milk has not been studied. Use of DFEs to determine a folate requirement for the infant would not be desirable.

Table 1. Recommended Dietary Allowance for Folate in Dietary Folate Equivalents (DFEs)

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	65 (AI)	65 (AI)
Infants	7-12 months	80 (AI)	80 (AI)
Children	1-3 years	150	150
Children	4-8 years	200	200
Children	9-13 years	300	300
Adolescents	14-18 years	400	400
Adults	19 years and older	400	400
Pregnancy	all ages	-	600
Breast-feeding	all ages	-	500

Genetic variation in folate requirements

A common polymorphism or variation in the sequence of the gene for the enzyme, 5, 10-methylenetetrahydrofolate reductase (MTHFR), known as the *MTHFR* c.677C>T polymorphism, results in a thermolabile enzyme (19). The substitution of a cytosine (C) by a thymine (T) at nucleotide 677 in the exon 4 of *MTHFR* gene leads to an alanine-to-valine transition in the catalytic domain of the enzyme. Depending on the population, 20% to 53% of individuals may have inherited one T copy (677C/T genotype), and 3% to 32% of individuals may have inherited two T copies (677T/T genotype) for the *MTHFR* gene (20). MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate (5,10-methylene THF) into 5-methyl tetrahydrofolate (5-MeTHF). The latter is the folate coenzyme required to form methionine from homocysteine (see **Figure 2** above). MTHFR activity is greatly diminished in heterozygous 677C/T (-30%) and homozygous 677T/T (-65%) individuals compared to those with the 677C/C genotype (21). Homozygosity for the mutation (677T/T) is linked to lower concentrations of folate in red blood cells and higher blood concentrations of homocysteine (22, 23). Improving folate nutritional status in elderly women with the T allele reduced plasma homocysteine concentration (24). An important unanswered question about folate is whether the present RDA is enough to compensate for the reduced MTHFR enzyme activity in individuals with at least one T allele, or whether those individuals have a higher folate requirement than the RDA (25).

Disease Prevention

Adverse pregnancy outcomes

Neural tube defects

Fetal growth and development are characterized by widespread cell division. Adequate folate is critical for DNA and RNA synthesis. Neural tube defects (NTDs) arise from failure of embryonic neural tube closure between the 21st and 27th days after conception, a time when many women may not even realize they are pregnant (26). NTDs include various malformations, such as lesions of the brain (e.g., anencephaly, encephalocele) or lesions of the spine (spina bifida), which are devastating and life-threatening (27). The prevalence of NTDs in the United States prior to fortification of food with folic acid was estimated to be 1 per 1,000 pregnancies (1). Results of randomized trials have demonstrated 60% to 100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the periconceptional period (about one month before and at least one month after conception) (28, 29). The results of these and other studies prompted the US Public Health Service to recommend that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent NTDs. Women with a previously affected pregnancy were also advised to receive 4,000 μg (4 mg) of folic acid daily in order to reduce NTD recurrence (30). These recommendations were made to all women of childbearing age because adequate folate must be available very early in pregnancy, and because many pregnancies in the US are unplanned (31).

Despite the effectiveness of folic acid supplementation in improving folate status, it appears that globally only 30% of women who become pregnant correctly follow the recommendation, and there is some concern that young women from minority ethnic groups and lower socioeconomic backgrounds are the least likely to follow the recommendation (32-34). To decrease the incidence of NTDs, the US FDA implemented legislation in 1998 requiring the fortification of all enriched grain products with 1.4 mg of folic acid per kg of grain (see Sources). The required level of folic acid fortification in the US was initially estimated to provide 100 μg of additional folic acid in the average person's diet, though it probably provides even more due to overuse of folic acid by food manufacturers (25, 35). The National Birth Defects Prevention Network reported about a 30% decrease in the prevalence of NTDs in the US compared to the pre-fortification period, and the post-fortification prevalence of NTDs is 0.69 cases per 1,000 live births and fetal deaths (36).

Also, a genetic component in NTD etiology is evidenced by the increased risk in women with a family history of an NTD and also by variations in risk among ethnicities (37). Moreover, NTD occurrence can be attributed to specific folate-gene interactions. The *MTHFR* c.677C>T polymorphism and other genetic variations can increase the folate requirement and susceptibility for an NTD-affected pregnancy. Prior to the fortification era, a case-control study showed that both red blood cell and serum folate concentrations were significantly lower in pregnant women with the T/T and C/T variants compared to the wild-type C/C genotype (22), suggesting inadequate folate metabolism with specific maternal genotypes. A meta-analysis of 25 case-control studies, including 2,429 case mothers and 3,570 control mothers, showed a positive association between the maternal *MTHFR* c.677C>T polymorphism and NTDs (38). Another *MTHFR* variant, an A-to-C change at position 1298, has also been associated with reduced MTHFR activity and increased NTD risk (39). Individuals heterozygous for both of these *MTHFR* variants (677C/T + 1298A/C) exhibit lower plasma folate and higher homocysteine concentrations than individuals with 677C/T + 1298A/A (40). Combined genotypes with homozygosity G/G for the reduced folate carrier transporter (*RFC-1*) polymorphism (c.80A>G) could further contribute to NTD occurrence (41). The degree of NTD risk was also assessed with additional *MTHFR* polymorphisms (c.116C>T, c.1793G>A) (42), as well as with mutations affecting other enzymes of the one-carbon metabolism, including methionine synthase (*MTR* c.2756A>G) (43), methionine synthase reductase (*MTRR* c.66A>G) (44), and methylenetetrahydrofolate dehydrogenase (*MTHFD1* c.1958G>A) (45). While maternal genotype can impact pregnancy outcome, it appears that gene-gene interactions between mother and fetus influence it further. The risk of NTD was increased by certain genetic combinations, including maternal (*MTHFR* c.677C>T)-fetal (*MTHFR* c.677C>T) and maternal (*MTRR* c.66A>G)-fetal (*MTHFR* c.677C>T) interactions (43, 44, 46). Finally, vitamin B_{12} status has been associated with NTD risk modification in the presence of specific polymorphisms in one-carbon metabolism (47).

Cardiovascular malformations

Congenital anomalies of the heart are a major cause of infant mortality but also cause deaths in adulthood (48). Using data from the European Registration of Congenital Anomalies and Twins (EUROCAT) database, a case-control study, involving 596 cases and 2,359 controls, found that consumption of at least 400 μg/day of folic acid during the periconceptual period (one month before conception through eight weeks' post-conception, covering the period of embryonic heart development) was associated with an 18% reduced risk of congenital heart defects (49). Recent meta-analyses of 20 to 25 case-control and family-based studies observed positive associations between maternal, fetal, or paternal *MTHFR* c.677C>T variant and incidence of congenital heart defects (50, 51). Additional studies are needed to elucidate the effects of gene-nutrient interactions on the risk of congenital heart defects; however, the currently available research indicates that adequate folate intake may play an important role.

Orofacial clefts

Maternal folate status during pregnancy may influence the risk of congenital anomalies called orofacial clefts, namely cleft lip with or without cleft palate (CL/P) (52). A population-based case-control study in Norway investigated the impact of folic acid supplements in mothers of 377 newborns with CL/P, 196 with cleft palate only (CPO) and 763 controls (53). Although dietary intakes or supplements (during the first three months of pregnancy) on their own did not significantly modify the risk of CL/P, the study reported a 64% lower risk among women taking multivitamin and folic acid (≥400 μg daily) supplements in addition to dietary folates. In the same population, polymorphisms in the cystathionine β-synthase (*CBS*) gene (c.699C>T) or *MTHFR* gene (c.677C>T; when folate intake was below 400 μg/day) appeared protective, while other gene variants in the folate/one-carbon metabolism could not be linked to CL/P (54, 55). However, a recent meta-analysis of 18 studies showed an elevation of CL/P risk with the maternal 677T/T homozygosity (56). Additional studies are needed to evaluate the risk of CL/P while integrating both genetic polymorphism and folate intake parameters. Epidemiological evidence supporting a role for folate in the risk of CPO is lacking.

Other adverse pregnancy outcomes

Low birth weight has been associated with increased risk of mortality during the first year of life and may also influence health outcomes during adulthood (57). A recent systematic review and meta-analysis of eight randomized controlled trials found a positive association between folic acid supplementation and birth weight; no association with length of gestation was observed (58). Additionally, a prospective cohort study of 306 pregnant adolescents associated low folate intakes and maternal folate status during the third trimester of pregnancy with higher incidence of small for gestational age births (birth weight <10th percentile) (59). Moreover, the maternal c.677C>T *MTHFR* genotype and increased homocysteine concentrations, considered an indicator of functional folate deficiency, have been linked to lower birth weights (60).

Elevated blood homocysteine concentrations have also been associated with increased incidence of miscarriage and other pregnancy complications, including preeclampsia and placental abruption (61). A large retrospective study showed that plasma homocysteine in Norwegian women was strongly related to adverse outcomes and complications, including preeclampsia, premature delivery, and very low birth weight, in previous pregnancies (62). A recent meta-analysis of 51 prospective cohort studies linked the c.677C>T *MTHFR* variant with increased risk of preeclampsia in Caucasian and East Asian populations, reinforcing the notion that folate metabolism may play a role in the condition (63). A large multicenter, randomized, controlled trial, the Folic Acid Clinical Trial (FACT), has been initiated to evaluate whether the daily supplementation of up to 5.1 mg of folic acid throughout pregnancy could prevent preeclampsia and other adverse outcomes (e.g., maternal death, placental abruption, preterm delivery) in high-risk women (64). Adequate folate intake during pregnancy protects against megaloblastic anemia (65). A recent case-control study found a reduction in risk of autism spectrum disorders with daily folic acid consumption of 600 μg or more before and during pregnancy when mother and child carried the c.677C>T *MTHFR* genotype (66).

Thus, it is reasonable to maintain folic acid supplementation throughout pregnancy, even after closure of the neural tube, in order to decrease the risk of other problems during pregnancy. Moreover, recent systematic reviews of observational studies found no evidence of an association between folate exposure during pregnancy and adverse health outcomes in offspring, in particular childhood asthma and allergies (67, 68).

Cardiovascular disease

Homocysteine and cardiovascular disease

The results of more than 80 studies indicate that even moderately elevated concentrations of homocysteine in the blood increase the risk of cardiovascular disease (CVD) (4). Possible predispositions to vascular accidents have also been linked to genetic deficiencies in homocysteine metabolism in certain populations (69). The mechanism by which homocysteine may increase the risk of vascular disease has been the subject of a great deal of research, but it may involve adverse effects of homocysteine on blood clotting, arterial vasodilation, and thickening of arterial walls (70). Although increased homocysteine concentrations in the blood have been consistently associated with increased risk of CVD, it is unclear whether lowering circulating homocysteine will reduce CVD risk (see Folate and homocysteine). Research had initially predicted that a prolonged decrease in serum homocysteine level of 3 micromoles/liter would lower the risk of CVD by up to 25% and be a reasonable treatment goal for individuals at high risk (71, 72). However, the analysis of recent clinical trials of B-vitamin supplementation has shown that lowering homocysteine concentrations did not prevent the occurrence of a second cardiovascular event in patients with existing CVD (73, 74). Consequently, the American Heart Association recommends screening for elevated total homocysteine concentrations only in "high risk" individuals, for example, in those with personal or family history of premature cardiovascular disease, malnutrition or malabsorption syndromes, hypothyroidism, kidney failure, lupus, or individuals taking certain medications (nicotinic acid, theophylline, bile acid-binding resins, methotrexate, and L-dopa).

Folate and homocysteine

Folate-rich diets have been associated with decreased risk of CVD, including coronary artery disease, myocardial infarction (heart attack), and stroke. A study that followed 1,980 Finnish men for 10 years found that those who consumed the most dietary folate had a 55% lower risk of an acute coronary event when compared to those who consumed the least dietary folate (75). Of the three B-vitamins that regulate homocysteine concentrations, folic acid has been shown to have the greatest effect in lowering basal concentrations of homocysteine in the blood when there is no coexisting deficiency of vitamin B_{12} or vitamin B_6 (see Nutrient interactions) (76). Increasing folate intake through folate-rich food or supplements has been found to reduce homocysteine concentrations (77). Besides, blood homocysteine concentrations have declined since the FDA mandated folic acid fortification of the grain supply in the US (25). A meta-analysis of 25 randomized controlled trials, including almost 3,000 subjects, found that folic acid supplementation with 800 μg/day or more could achieve a maximal 25% reduction in plasma homocysteine concentrations. In this meta-analysis, daily doses of 200 μg and 400 μg of folic acid were associated with a 13% and 20% reduction in plasma homocysteine, respectively (78). A supplement regimen of 400 μg of folic acid, 2 mg of vitamin B_6, and 6 μg of vitamin B_{12} has been advocated by the American Heart Association if an initial trial of a folate-rich diet (see Sources) is not successful in adequately lowering homocysteine concentrations (79).

Several polymorphisms in folate/one-carbon metabolism modify homocysteine concentrations in blood (80). In particular, the effect of the c.677C>T *MTHFR* variant has been examined in relation to folic acid fortification policies worldwide. The analysis of randomized trials, including 59,995 subjects without a history of CVD, revealed that the difference in homocysteine concentrations between T/T and C/C genotypes was greater in low-folate regions compared to regions with food fortification policy (3.12 vs. 0.13 micromoles/liter) (81). Although folic acid supplementation effectively decreases homocysteine concentrations, it is not yet clear whether it also decreases risk for CVD. A recent meta-analysis of 19 randomized clinical trials, including 47,921 subjects with preexisting cardiovascular or renal disease, found that homocysteine lowering through folic acid and other B-vitamin supplementation failed to reduce the incidence of CVD despite significant reductions in plasma homocysteine concentrations (74). Other meta-analyses have confirmed the lack of causality between the lowering of homocysteine and the risk of CVD (80-82), including the risk of stroke (83, 84). Consequently, the American Heart Association removed its recommendation for using folic acid to prevent cardiovascular disease in high-risk women (85). It should be noted that the majority of prevention trials to date have been performed in CVD patients with advanced disease. The evidence supporting a beneficial role for folate and related B-vitamins appears to be strongest for the primary prevention of stroke (86). The introduction of mandatory folic acid fortification has been associated with a decline in stroke-related mortality in North America, adding further support to the potential benefit of enhancing folate status and/or lowering homocysteine in the prevention of stroke (87).

Despite the controversy regarding the role of homocysteine lowering in CVD prevention, some studies have investigated the effect of folic acid supplementation on the development of atherosclerosis, a known risk factor for vascular accidents. The measurement of the carotid intima-media thickness (CIMT) is a surrogate endpoint for early atherosclerosis and a predictor for cardiovascular events (88). The meta-analysis of 10 randomized trials testing the effect of folic acid supplementation showed a significant reduction in CIMT in subjects with chronic kidney diseases and in those at high risk for CVD, but not in healthy participants (89). Endothelial dysfunction is a common feature in atherosclerosis and vascular disease. High doses of folic acid (400-10,000 μg/day) have been associated with improvements in vascular health in both healthy and CVD subjects (90). Although recent trials failed to demonstrate any cardiovascular protection from folic acid supplementation, low folate intake is a known risk factor for vascular disease, and more research is needed to explore the role of folate in maintaining vascular health (91).

Cancer

Cancer is thought to arise from DNA damage in excess of ongoing DNA repair and/or the inappropriate expression of critical genes. Because of the important roles played by folate in DNA and RNA synthesis and methylation, it is possible that inadequate folate intake contributes to genome instability and chromosome breakage that often characterize cancer development. In particular, DNA replication and repair are critical for genome maintenance, and the shortage in nucleotides caused by folate deficiency might lead to genome instability and DNA mutations. A decrease in 5,10-methylene THF can compromise the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) by the enzyme thymidylate synthase (TS), causing uracil accumulation and thymine depletion. This could then lead to uracil misincorporation into DNA during replication or repair, and cause DNA damage, including point mutations and strand breaks (92). Since 5,10-methylene THF is also the MTHFR enzyme substrate, it is plausible that a reduction of MTHFR activity with the c.677C>T polymorphism may increase the use of 5,10-methylene THF for thymidylate synthesis and prevent DNA damage. However, this hypothesis might only be valid in a situation of folate deficiency (93). Conversely, it was argued that folic acid supplementation could fuel DNA synthesis, therefore promoting tumor growth. This is supported by the observation that TS can function like a tumor promoter (oncogene), while a reduction in TS activity is linked to a lower risk of cancer (94, 95). Additionally, antifolate molecules that block the thymidylate synthesis pathway are successfully used in cancer therapy (96). Folate also controls the homocysteine/methionine cycle and the pool of S-adenosylmethionine (SAM), the methyl donor for methylation reactions. Thus, folate deficiency may impair DNA and protein methylation and alter the expression of genes involved in DNA repair, proliferation and cell death. Global DNA hypomethylation, a typical hallmark of cancer, causes genome instability and chromosome breaks (reviewed in 97).

The consumption of at least five servings of fruit and vegetables daily has been consistently associated with a decreased incidence of cancer (98). Fruit and vegetables are excellent sources of folate, which may play a role in their anti-carcinogenic effect. Observational studies have found diminished folate status to be associated with site-specific cancers. While food fortification is mandatory in the US (since 1998; see Sources), concerns about the impact of high folic acid intakes on health have delayed the practice in several other countries (99). However, the most recent meta-analyses of folic acid intervention trials (supplemental doses ranging from 500 to 5,000 μg/day for at least one year) did not show any specific benefit or harm regarding total and site-specific cancer incidence (100, 101).

Colorectal cancer

A pooled analysis of 13 prospective cohort studies, which followed a total of 725,134 individuals for a 7 to 20-year period, revealed a modest, inverse association between dietary and total (from food and supplements) folate intake and colon cancer risk. Specifically, a 2% decrease in colon cancer risk was estimated for every 100 μg/day increase in total folate intake (102). A large US prospective study, which followed 525,488 subjects, ages 50 to 71 years between 1995 and 2006, correlated dietary folate, supplemental folic acid, and total folate intakes with a decreased colorectal cancer (CRC) risk (103). However, when stratified by gender, there was no association between dietary folate intake and CRC risk in women (103, 104). A lack of association between CRC risk and dietary, supplemental, and total folate intakes was also reported in another prospective study that followed more than 90,000 US postmenopausal women during an 11-year period encompassing pre- and post-fortification periods (105). These data suggest the possible influence of gender over CRC risk modification by folate. In the latter study, a significant but transient risk elevation was also observed during the post-fortification era; however, some have asserted that this is unlikely to be caused by increased folate intake due to mandatory fortification (106). Finally, a meta-analysis of 18 case-control studies found a slight reduction in CRC risk with folate from food (107). However, it is important to note that the case-control studies were highly heterogeneous, and that the authors stated that dietary fiber, vitamins, and alcohol intake could have confounded their results. Moreover, the lower limit of the highest quantile of folate intake was highly variable, ranging from 270 to 1,367 μg/day (107).

While most epidemiological research shows a protective effect of folate against colorectal cancer development, it has been suggested that high doses of supplemental folic acid may actually accelerate tumor growth in cancer patients (108). Whereas higher folate status within the normal dietary range is widely considered to be protective against cancer, some investigators remain concerned that exposure to excessively high folic acid intakes may increase the growth of pre-existing neoplasms (108). Several clinical trials addressed the effect of folic acid supplementation in patients with a history of colorectal adenoma, with trials finding a risk reduction or no effect of supplemental folic acid (109-112). A recent meta-analysis of three large randomized controlled trials in high-risk subjects did not demonstrate any increase in colorectal adenoma recurrence in subjects supplemented with 500 or 1,000 μg/day of folic acid for 24 to 42 months when compared with placebo treatment (113).

As suggested earlier, the *MTHFR* 677T/T genotype might prevent uracil misincorporation and protect DNA integrity and stability under low-folate conditions. A meta-analysis of 62 case-control and two cohort studies revealed that while the T/T variant reduces CRC risk by 12% compared to both C/T and C/C genotypes, the risk was decreased by 30% with high (348-1,583 μg/day) versus low total folate intakes (264-450 μg/day), irrespective of the genotype (114). A common polymorphism (c.2756A>G) in the *MTR* gene, which codes for methionine synthase, was also examined in relation with the risk of colorectal adenoma and cancer. Methionine synthase catalyzes the simultaneous conversion of homocysteine and 5-methylene THF into methionine and TFH, respectively. The recent meta-analysis of 27 case-control studies showed no association between *MTR* variant and cancer risk (115).

Although alcohol consumption interferes with the absorption and metabolism of folate (16), one case-control and five prospective cohort studies have reported either reduction in CRC risk among nondrinkers compared to drinkers or a lack of association (107). However, in a large prospective study that followed more than 28,000 male health professionals for 22 years, intake of more than two alcoholic drinks (>30 grams of alcohol) per day augmented CRC risk by 42% during the pre-fortification period. CRC risk was not increased during the post-fortification period, suggesting that it is the combination of high alcohol and low folate intake that might increase CRC risk. Yet, another prospective study that followed more than 69,000 female nurses for 28 years did not report a significant increase in CRC risk with alcohol intake before and after the mandatory folic acid fortification (116). In some studies, individuals who are homozygous for the c.677C>T *MTHFR* polymorphism (T/T) have been found to be at decreased risk for colon cancer when folate intake is adequate. However, when folate intake is low and/or alcohol intake is high, individuals with the (T/T) genotype have been found to be at increased risk of colorectal cancer (117, 118).

Breast cancer

Several prospective cohort and case-control studies investigating whether folate intake affects breast cancer risk have reported mixed results (119). A meta-analysis of 15 prospective studies and one nested case-control study found no relationship with dietary folate intake (120). Moderate alcohol intake has been associated with increased risk of breast cancer in women (121). The results of three prospective studies suggested that increased folate intake may reduce the risk of breast cancer in women who regularly consume alcohol (122-124). Thus, high folate intake might be associated with a risk reduction only in women whose breast cancer risk is raised by alcohol consumption. A very large prospective study in more than 88,000 nurses reported that folic acid intake was not associated with breast cancer in women who consumed less than one alcoholic drink per day. However, in women consuming at least one alcoholic drink per day, folic acid intake of at least 600 μg daily resulted in about half the risk of breast cancer compared with women who consumed less than 300 μg of folic acid daily (124). Nevertheless, whether and how alcohol consumption increases breast cancer risk is still subject to discussion (125, 126). Finally, recent meta-analyses evaluating the influence of polymorphisms in one-carbon metabolism on cancer risk found that specific variants in the gene encoding thymidylate synthase increased the risk of breast cancer in certain ethnic populations (127, 128).

Childhood cancers

The incidence of Wilms' tumors (kidney cancer) and certain types of brain cancers (neuroblastoma, ganglioneuroblastoma, and ependymoma) in children has decreased since the mandatory fortification of the US grain supply in 1998 (129). However, incidence rates were unchanged between the pre- and post-fortification periods for leukemia—a predominant childhood malignancy. Despite earlier studies linking maternal folic acid supplementation during pregnancy with the reduced risk of childhood leukemia, more recent investigations have found little evidence to support a preventive effect of folic acid (130). Several meta-analyses have also found little to no protective effect with *MTHFR* polymorphisms; however, the most recent meta-analysis of 22 case-control studies found a reduction in the risk of acute lymphoblastic leukemia (ALL) with the c.677C>T variant in Caucasians and Asians (131).

Alzheimer's disease and cognitive impairment

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5 million individuals over 65 years old in the US (132). β-amyloid plaque deposition, Tau protein-forming tangles, and increased cell death in the brain of AD patients have been associated with cognitive decline and memory loss. One study associated increased consumption of fruit and vegetables, which are abundant sources of folate, with a reduced risk of developing dementia and AD in women (133). Through its role in nucleic acid synthesis and methyl donor provision for methylation reactions, folate is critical for normal brain development and function, not only during pregnancy and after birth, but also later in life (134). In one cross-sectional study of elderly women, AD patients had significantly higher homocysteine and lower red blood cell folate concentrations compared to healthy individuals. However, there was no difference in the level of serum folate between groups, suggesting that long-term folate status, rather than recent folate intake, may be associated with the risk of AD (135).

Several investigators have described associations between increased homocysteine concentrations and cognitive impairment in the elderly (136), but prospective cohort studies have not found higher folate intakes to be associated with improved cognition (137, 138). Higher homocysteine concentrations were found in individuals suffering from dementia, including AD and vascular dementia, compared to healthy subjects (139, 140). Although deficiencies in folate, vitamin B_{12}, and vitamin B_6 could increase homocysteine concentrations, a reduction in vitamin concentrations in the serum of AD patients compared to healthy individuals could not be attributed to decreased vitamin intakes (141). It is not presently clear whether serum homocysteine is a risk factor for developing dementia or simply associated with the cognitive decline. In the last decade, a number of clinical trials have tested the use of B-vitamins to lower homocysteine and prevent or delay cognitive decline. A meta-analysis of nine randomized, placebo-controlled trials of folic acid supplementation (0.2 to 15 mg/day for a median duration of six months) in healthy individuals over 45 years of age failed to find a short-term effect on cognitive functions, including memory, speed, language, and executive functions (142). More recently, a meta-analysis of 19 randomized, placebo-controlled trials of B-vitamin supplementation found no difference in cognitive parameters between the treatment and placebo groups, despite the treatment effectively lowering homocysteine concentrations (143). Inconsistent findings across trials may be due to differences in design and methodology (reviewed in 144).

Nevertheless, a two-year randomized, placebo-controlled trial in 168 elderly subjects with mild cognitive impairment recently described the benefits of a daily regimen of 800 μg of folic acid, 500 μg of vitamin B_{12}, and 20 mg of vitamin B_6 (145, 146). Atrophy of specific brain regions affected by AD was observed in individuals of both groups, and this atrophy correlated with cognitive decline; however, the B-vitamin treatment group experienced a smaller loss of gray matter compared to the placebo group (0.5% vs. 3.7%). A greater benefit was seen in subjects with higher baseline homocysteine concentrations, suggesting the importance of lowering circulating homocysteine in prevention of cognitive decline and dementia. Although encouraging, the effect of B-vitamin supplementation needs to be further studied in larger trials that evaluate long-term outcomes, such as the incidence of AD.

Disease Treatment

Metabolic diseases

Folinic acid (see **Figure 1** above), a tetrahydrofolic acid derivative, is used in the clinical management of rare inborn errors that affect folate transport or metabolism (reviewed in 147). Such conditions are of autosomal recessive inheritance, meaning only individuals receiving two copies of the mutated gene (one from each parent) develop the disease.

Hereditary folate malabsorption

Hereditary folate malabsorption is caused by mutations in the *SLC46A1* gene coding for the folate transporter PCFT and typically affects gastrointestinal folate absorption and folate transport into the brain (148). Patients present with low to undetectable concentrations of folate in serum and cerebrospinal fluid, pancytopenia (low number of all blood cells), impaired immune responses that increase susceptibility to infections, and a general failure to thrive (149). Neurologic symptoms, including seizures, have also been observed (150). Clinical improvements have been recorded following parenteral provision of folinic acid (151).

Cerebral Folate Deficiency (CFD) syndrome

CFD is characterized by low levels of folate coenzymes in cerebrospinal fluid despite normal concentrations of folate in blood. Folate transport across the blood-brain barrier is compromised in CFD and has been linked either to the presence of antibodies blocking the folate receptor FRα or to mutations in the *FOLR1* gene encoding FRα (152, 153). Neurologic abnormalities, along with visual and hearing impairments, have been described in children with CFD; autism spectrum disorder (ASD) is present in some cases. Folinic acid (also known as leucovorin) can enter the brain and normalize the level of folate coenzymes and has been shown to normalize folate concentrations and improve various social interactions in CFD, including mood, behavior, and verbal communication in children with ASD (152, 154, 155).

Dihydrofolate reductase (DHFR) deficiency

DHFR is the NADPH-dependent enzyme that catalyzes the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). DHFR is also required to convert folic acid to DHF. DHFR deficiency is characterized by megaloblastic anemia and cerebral folate deficiency causing intractable seizures and mental deficits. Although folinic acid treatment can alleviate the symptoms of DHFR deficiency, early diagnosis is essential to prevent irreversible brain damage and improve clinical outcomes (156, 157).

Sources

Food sources

Green leafy vegetables (foliage) are rich sources of folate and provide the basis for its name. Citrus fruit juices, legumes, and fortified foods are also excellent sources of folate (1); the folate content of fortified cereal varies greatly. A number of folate-rich foods are listed in **Table 2**, along with their folate content in micrograms (μg). For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Folate and Folic Acid

Food	Serving	Folate (μg DFEs)
Lentils (mature seeds, cooked, boiled)	½ cup	179
Garbanzo beans (chickpeas, cooked, boiled)	½ cup	141
Asparagus (cooked, boiled)	½ cup (~6 spears)	134
Spinach (cooked, boiled)	½ cup	131
Lima beans (large, mature seeds, cooked, boiled)	½ cup	78
Orange juice (raw)	6 fl. oz.	56
Spaghetti (enriched, cooked)	1 cup	167*
White rice (enriched, cooked)	1 cup	153*
Bread (enriched)	1 slice	84*

*To help prevent neural tube defects, the US FDA required the addition of 1.4 milligrams (mg) of folic acid per kilogram (kg) of grain to be added to refined grain products, which are already enriched with niacin, thiamin, riboflavin, and iron, as of January 1, 1998. The addition of nutrients to food in order to prevent a nutritional deficiency or restore nutrients lost in processing is known as fortification. The FDA initially estimated that this level of fortification would increase dietary intake by an average of 100 µg folic acid/day (26). However, further evaluations based on observational studies suggested increases twice that predicted by the FDA (35). The prevalence of low folate concentrations in both serum and red blood cells is currently below 1% in the US population, compared to 24% and 3.5%, respectively, before the fortification period (158).

Supplements

The principal form of supplementary folate is folic acid. It is available in single-ingredient and combination products, such as B-complex vitamins and multivitamins. Doses of 1 mg or greater require a prescription (159). Additionally, folinic acid, a tetrahydrofolic acid derivative, is used to manage certain metabolic diseases (see Disease Treatment). Further, the US FDA has approved the supplementation of folate in oral contraceptives. The addition of levomefolate calcium (the calcium salt of MeTHF; 451 µg/tablet) to oral contraceptives is intended to raise folate status in women of childbearing age (160). According to a US national survey, only 24% of non-pregnant women aged 15-44 years are meeting the current recommendation of 400 µg/day of folic acid (161).

Safety

Toxicity

No adverse effects have been associated with the consumption of excess folate from food. Concerns regarding safety are limited to synthetic folic acid intake. Deficiency of vitamin B_{12}, though often undiagnosed, may affect a significant number of people, especially older adults (see the article on Vitamin B_{12}). One symptom of vitamin B_{12} deficiency is megaloblastic anemia, which is indistinguishable from that associated with folate deficiency (see Deficiency). Large doses of folic acid given to an individual with an undiagnosed vitamin B_{12} deficiency could correct megaloblastic anemia without correcting the underlying vitamin B_{12} deficiency, leaving the individual at risk of developing irreversible neurologic damage. Such cases of neurologic progression in vitamin B_{12} deficiency have been mostly seen at folic acid doses of 5,000 µg (5 mg) and above. In order to be very sure of preventing irreversible neurological damage in vitamin B_{12}-deficient individuals, the Food and Nutrition Board of the US Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 µg (1 mg) daily (**Table 3**). The Board also noted that vitamin B_{12} deficiency is very rare in women in their childbearing years, making the consumption of folic acid at or above 1,000 µg/day unlikely to cause problems (1); however, there are limited data on the effects of large doses.

Table 3. Tolerable Upper Intake Level (UL) for Folic Acid

Age Group	UL (µg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	300
Children 4-8 years	400
Children 9-13 years	600
Adolescents 14-18 years	800
Adults 19 years and older	1,000
*Source of intake should be from food and formula only.	

The saturation of DHFR metabolic capacity by oral doses of folic acid has been associated with the appearance of unmetabolized folic acid in blood (162). Hematologic abnormalities and poorer cognition have been associated with the presence of unmetabolized folic acid in vitamin B_{12}-deficient older adults (≥60 years) (163, 164). A small study conducted in postmenopausal women also raised concerns about the effect of exposure to unmetabolized folic acid on immune function (165). In a small, randomized, open-label trial in 38 women of reproductive age receiving 30 weeks of daily multivitamin supplements, daily supplementation with either 1.1 mg or 5 mg of folic acid resulted in the transient appearance of unmetabolized folic acid in blood over the first 12 weeks of supplementation (166). However, unmetabolized folic acid concentrations returned to baseline levels at the end of the study, suggesting that adaptive mechanisms eventually converted folic acid to reduced forms of folate. Nonetheless, the use of supplemental levomefolate (5-methyl THF) may provide an alternative to prevent the potential negative effects of unconverted folic acid in older adults.

Drug interactions

When nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, are taken in very large therapeutic dosages (i.e., to treat severe arthritis), they may interfere with folate metabolism. In contrast, routine use of NSAIDs has not been found to adversely affect folate status. The anticonvulsant, phenytoin, has been shown to inhibit the intestinal absorption of folate, and several studies have associated decreased folate status with long-term use of the anticonvulsants, phenytoin, phenobarbital, and primidone (167). However, few studies controlled for differences in dietary folate intake between anticonvulsant users and nonusers. Also, taking folic acid at the same time as the cholesterol-lowering agents, cholestyramine and colestipol, may decrease the absorption of folic acid (159). Methotrexate is a folate antagonist used to treat a number of diseases, including cancer, rheumatoid arthritis, and psoriasis. Some of the side effects of methotrexate are similar to those of severe folate deficiency, and supplementation with folic or folinic acid is used to reduce antifolate toxicity. Other antifolate molecules currently used in cancer therapy include aminopterin, pemetrexed, pralatrexate, and raltitrexed (96). Further, a number of other medications have been shown to have antifolate activity, including trimethoprim (an antibiotic), pyrimethamine (an antimalarial), triamterene (a blood pressure medication), and sulfasalazine (a treatment for ulcerative colitis). Early studies of oral contraceptives (birth control pills) containing high doses of estrogen indicated adverse effects on folate status; however, this finding has not been supported in more recent studies that used low-dose oral contraceptives and controlled for dietary folate (168).

Linus Pauling Institute Recommendation

The available scientific evidence shows that adequate folate intake prevents neural tube defects and other poor outcomes of pregnancy; is helpful in lowering the risk of some forms of cancer, especially in genetically susceptible individuals; and may lower the risk of cardiovascular disease. The Linus Pauling Institute recommends that adults take a daily multivitamin/mineral supplement, which typically contains 400 µg of folic acid, the Daily Value (DV). Even with a larger than average intake of folic acid from fortified food, it is unlikely that an individual's daily folic acid intake would regularly exceed the tolerable upper intake level of 1,000 µg/day established by the Institute of Medicine (see Safety).

Older adults (>50 years)

The recommendation for 400 µg/day of supplemental folic acid as part of a daily multivitamin/mineral supplement, in addition to a folate-rich diet, is especially important for older adults because blood homocysteine concentrations tend to increase with age (see Disease Prevention).

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  - Niacin-responsive genetic disorders
  - Cardiovascular disease
  - Friedreich's ataxia
  - HIV/AIDS
  - Schizophrenia
- Sources
  - Food
  - Supplements
- Safety
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Español

Summary

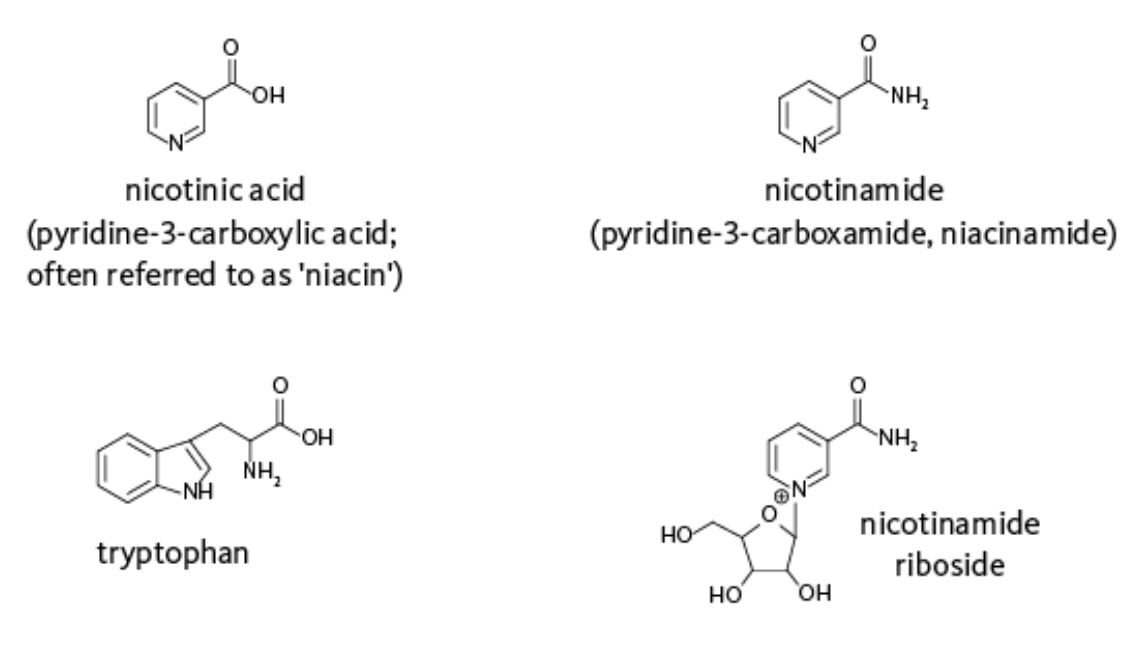
- Dietary precursors of nicotinamide adenine dinucleotide (NAD), including nicotinic acid, nicotinamide, and nicotinamide riboside, are collectively referred to as niacin or vitamin B_3. The essential amino acid tryptophan can also be converted into NAD via the kynurenine pathway. *(More information)*
- NAD can be phosphorylated (NADP) and reduced (NADH and NADPH). NAD functions in oxidation-reduction (redox) reactions and non-redox reactions. *(More information)*
- Pellagra is the disease of severe niacin deficiency. It is characterized by symptoms affecting the skin, the digestive system, and the nervous system; pellagra can lead to death if left untreated. *(More information)*
- Causes of niacin deficiency include inadequate oral intake, poor bioavailability from unlimed grains, defective tryptophan absorption, metabolic disorders, and the long-term use of chemotherapeutic treatments. *(More information)*
- Dietary intake requirements for niacin are based on the urinary excretion of niacin metabolites. *(More information)*
- NAD is the sole substrate for PARP enzymes and sirtuins involved in DNA repair activities; thus, NAD is critical for genome stability. Several studies, mostly using *in vitro* and animal models, suggest a possible role for niacin in cancer prevention. In a recent phase III trial, a daily pharmacologic dose of nicotinamide was found to reduce the rate of premalignant skin lesions and nonmelanoma cancers in high-risk subjects. *(More information)*
- Despite promising initial results, nicotinamide administration has failed to prevent or delay the onset of type 1 diabetes mellitus in high-risk relatives of type 1 diabetic patients. Future research might explore the use of nicotinamide in combined therapy and evaluate activators of NAD-dependent enzymes. *(More information)*
- At pharmacologic doses, nicotinic acid improved lipid profiles of patients with a history of vascular disease yet failed to reduce recurrent cardiovascular events or mortality. *(More information)*
- Elevated tryptophan breakdown in the kynurenine pathway and niacin deficiency have been reported in HIV-positive people. However, at present, a better understanding of the role of kynurenine pathway and other NAD biosynthetic pathways during HIV infection is needed to establish whether this population could benefit from niacin supplementation. *(More information)*
- Most adverse effects of niacin (nicotinic acid and nicotinamide) have been reported with pharmacological doses of nicotinic acid. The tolerable upper intake level (UL) for niacin is based on preventing skin flushing, nicotinic acid's most prominent side effect. The co-administration of laropiprant — a prostaglandin D2 receptor-1 antagonist — helps reduce nicotinic acid-induced skin flushing. *(More information)*

Niacin or vitamin B_3 is a water-soluble vitamin used by the body to form the nicotinamide coenzyme, NAD$^+$. The term 'niacin' is often used to refer to nicotinic acid (pyridine-3-carboxylic acid) only, although other vitamers with a pyridine ring, including nicotinamide (pyridine-3-carboxamide) and nicotinamide riboside, also contribute to NAD$^+$ formation (1). None of the vitamers are related to the nicotine found in tobacco, although their names are similar. Likewise, nicotine — but not nicotinic acid — is an agonist of the nicotinic receptors that respond to the neurotransmitter, acetylcholine.

Metabolism

Essential to all forms of life, the nicotinamide coenzyme NAD$^+$ is synthesized in the body from four precursors that are provided in the diet: nicotinic acid, nicotinamide, nicotinamide riboside, and tryptophan (**Figure 1**).

Figure 1. Precursors of Nicotinamide Adenine Dinucleotide (NAD$^+$) in the Diet



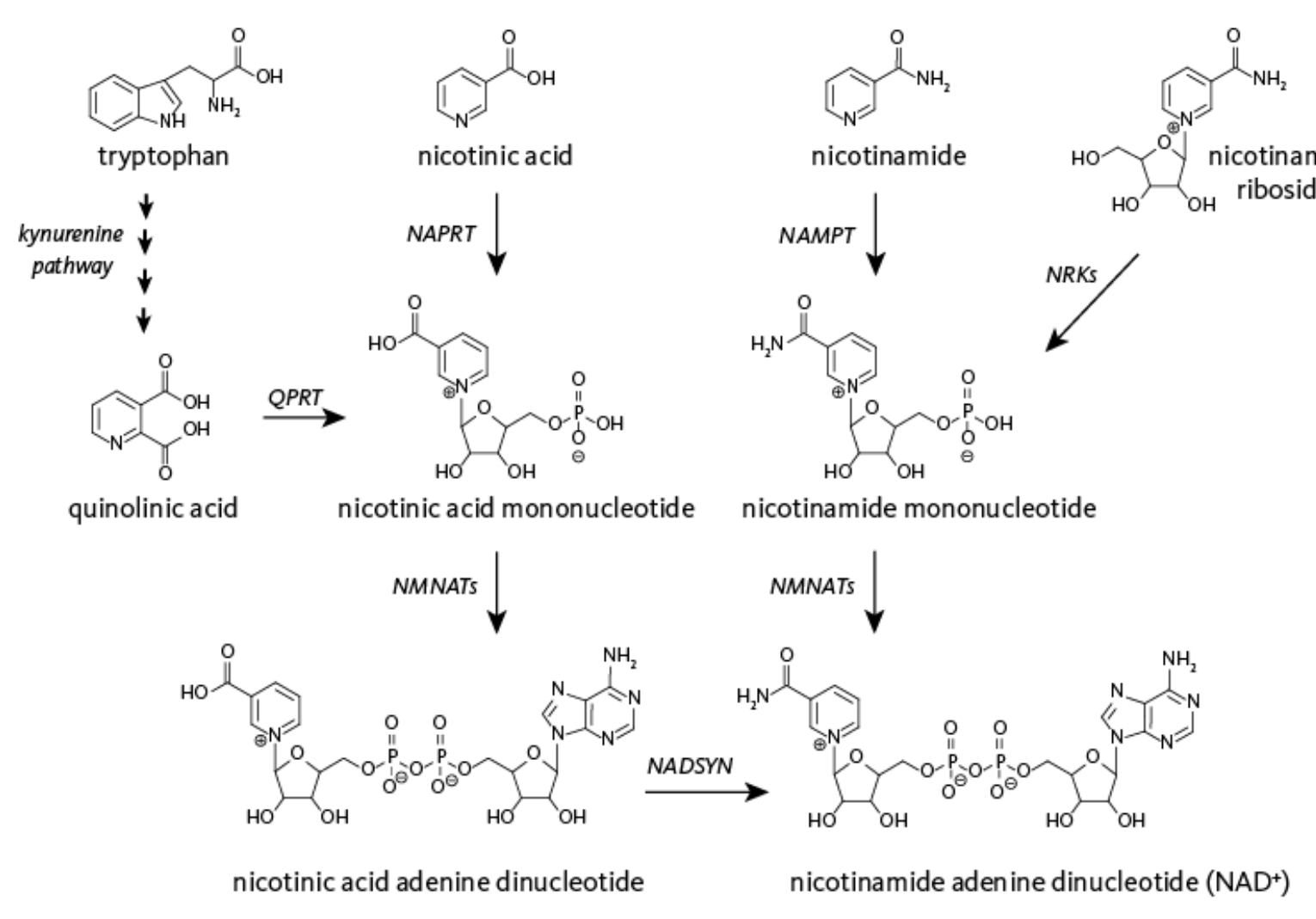
nicotinic acid
(pyridine-3-carboxylic acid;
often referred to as 'niacin')
nicotinamide
(pyridine-3-carboxamide, niacinamide)
tryptophan
nicotinamide
riboside

[Figure 1 - Click to Enlarge]

Figure 2 illustrates the separate biosynthetic pathways that lead to NAD$^+$ production from the various dietary precursors. NAD$^+$ is synthesized from nicotinamide and nicotinamide riboside via two enzymatic reactions, while the pathway that yields NAD$^+$ from nicotinic acid - known as the Preiss-Handler pathway — includes three steps. The kynurenine pathway is the longest NAD$^+$ biosynthetic pathway: the catabolism of tryptophan through kynurenine produces quinolinic acid, which is then converted to nicotinic acid mononucleotide, an intermediate in NAD$^+$metabolism. NAD$^+$ is then synthesized from nicotinic acid mononucleotide in the Preiss-Handler pathway (2).

All pathways generate intermediary mononucleotides — either nicotinic acid mononucleotide or nicotinamide mononucleotide. Specific enzymes, known as phosphoribosyltransferases, catalyze the addition of a phosphoribose moiety onto nicotinic acid or quinolinic acid to produce nicotinic acid mononucleotide or onto nicotinamide to generate nicotinamide mononucleotide. Nicotinamide mononucleotide is also generated by the phosphorylation of nicotinamide riboside, catalyzed by nicotinamide riboside kinases (NRKs). Further, adenylyltransferases catalyze the adenylation of these mononucleotides to form either nicotinic acid adenine dinucleotide or NAD$^+$. Nicotinic acid adenine dinucleotide is then converted to NAD$^+$ by glutamine-dependent NAD$^+$ synthetase (NADSYN), which uses glutamine as an amide group donor (**Figure 2**) (2). Of note, nicotinic acid adenine dinucleotide has been reported to form following the administration of high-dose nicotinamide riboside, suggesting that a potential deamidation could occur to convert NAD$^+$ to nicotinic acid adenine dinucleotide when the pool of NAD$^+$ is high (1).

Figure 2. Synthesis of Nicotinamide Adenine Dinucleotide (NAD$^+$)



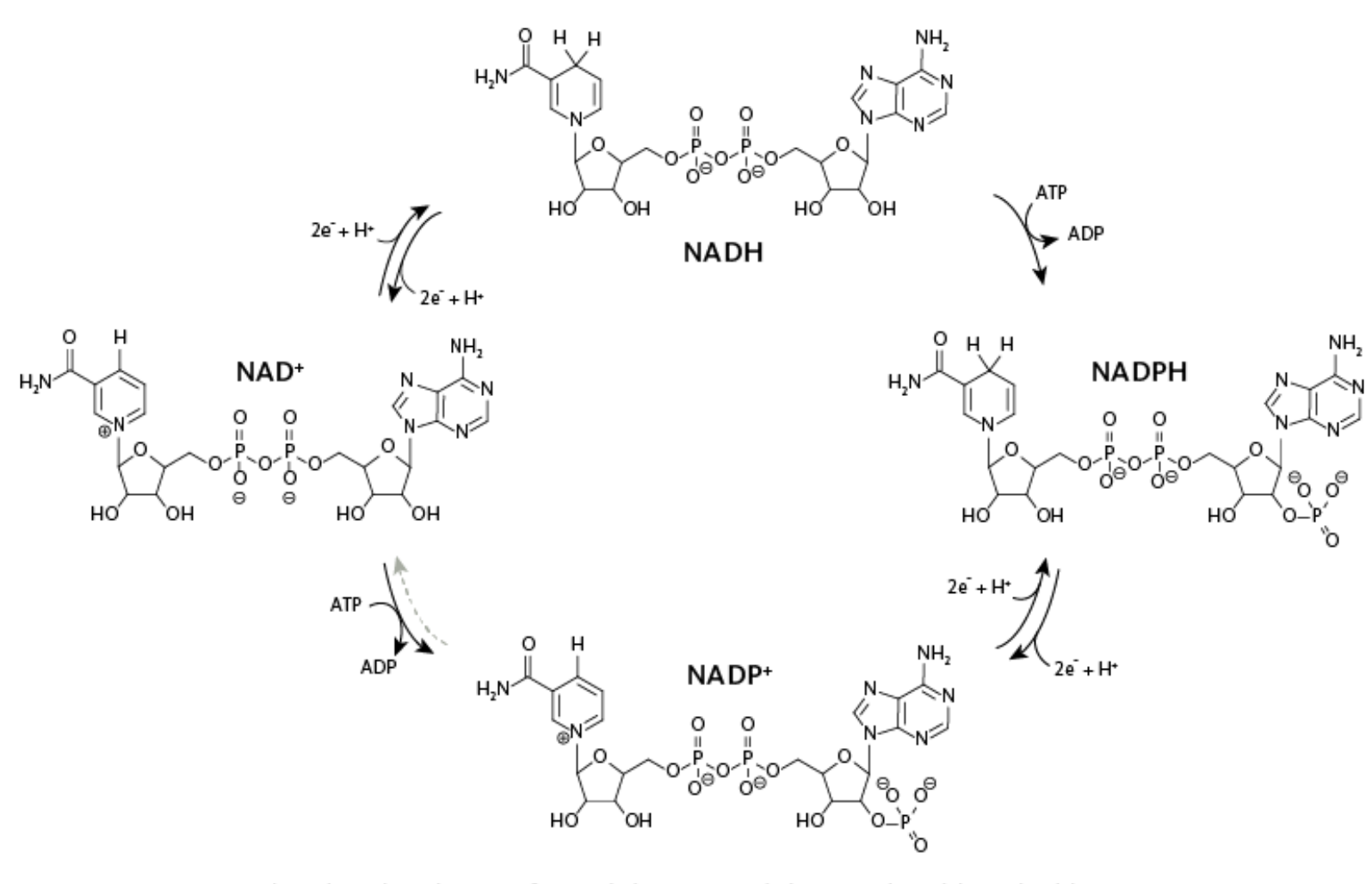
tryptophan
nicotinic acid
nicotinamide
nicotinamide riboside
kynurenine pathway
NAPRT
NAMPT
NRKs
QPRT
quinolinic acid
nicotinic acid mononucleotide
nicotinamide mononucleotide
NMNATs
NMNATs
NADSYN
nicotinic acid adenine dinucleotide
nicotinamide adenine dinucleotide (NAD+)

Tryptophan can be converted to quinolinic acid in the kynurenine pathway; QPRT catalyzes the conversion of quinolinic acid to nicotinic acid mononucleotide. Nicotinic acid mononucleotide is also the product of the reaction of phosphoribosylation of nicotinic acid catalyzed by NAPRT. Nicotinic acid mononucleotide is then converted to nicotinic acid adenine dinucleotide in a reaction catalyzed by NMNATs; NADSYN catalyzes the amidation of nicotinic acid adenine dinucleotide into NAD$^+$. Both nicotinamide and nicotinamide riboside are precursors of nicotinamide mononucleotide. The adenylation of nicotinamide mononucleotide catalyzed by NMNATs produces NAD$^+$. *NADSYN, Nicotinamide adenine dinucleotide synthase; NAMPT, Nicotinamide phosphoribosyltransferase; NAPRT, Nicotinic acid phosphoribosyltransferase; NMNATs, Nicotinamide mononucleotide adenylyltransferase; NRKs, Nicotinamide riboside kinases; QPRT, Quinolinate phosphoribosyltransferase.*

[Figure 2 - Click to Enlarge]

NAD kinase catalyzes the phosphorylation of NAD into NADP using adenosyl triphosphate (ATP) as the phosphoryl donor (3). The oxidation-reduction (redox) properties of the dinucleotide are not affected by the phosphorylation such that the redox pairs NAD$^+$/NADH and NADP$^+$/NADPH show similar redox potentials (4). Oxidation and reduction of the C-4 position of the nicotinamide moiety of NADand its phosphorylated form are essential for electron-transfer reactions supporting vital metabolic and bioenergetic functions in all cells (see Function). Thus, NAD and NADP are recycled back and forth between oxidized (NAD$^+$ and NADP$^+$) and reduced forms (NADH and NADPH), as shown in **Figure 3**.

Figure 3. NAD(P) Oxido-reduction Balance



The phosphorylation of NAD(H) to NADP(H) is catalyzed by a highly conserved enzyme, NAD kinase. Oxidoreductases catalyze the transfer of electrons and hydrogens between molecules using NAD(P)$^+$ and NAD(P)H as electron acceptors and donors, respectively. Thus, in electron-transfer reactions, dinucleotides are recycled back and forth between their oxidized (NAD$^+$ and NADP$^+$) and reduced (NADH and NADPH) forms.

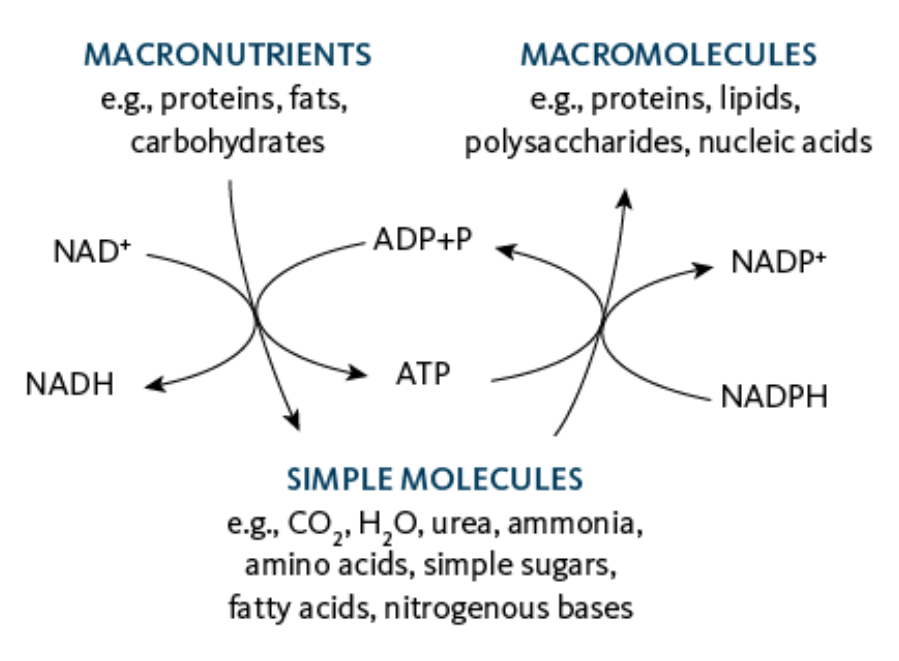
[Figure 3 - Click to Enlarge]

Function

NAD as a coenzyme in electron-transfer reactions

Living organisms derive most of their energy from redox reactions, which are processes involving the transfer of electrons. Over 400 enzymes require the niacin coenzymes, NAD and NADP, mainly to accept or donate electrons for redox reactions (5). NAD and NADP appear to support distinct functions (**Figure 4**). NAD functions most often in energy-producing reactions involving the degradation (catabolism) of carbohydrates, fats, proteins, and alcohol. NADP generally serves in biosynthetic (anabolic) reactions, such as in the synthesis of fatty acids, steroids (e.g., cholesterol, bile acids, and steroid hormones), and building blocks of other macromolecules (4). NADP is also essential for the regeneration of components of detoxification and antioxidant systems (4). To support these functions, the cell maintains NAD in a largely oxidized state (NAD$^+$) to serve as oxidizing agent for catabolic reactions, while NADP is kept largely in a reduced state (NADPH) to readily donate electrons for reductive cellular processes (4, 6).

Figure 4. Simplified Overview of NAD/NADP Function in Catabolic and Anabolic Pathways



MACRONUTRIENTS
e.g., proteins, fats, carbohydrates
MACROMOLECULES
e.g., proteins, lipids, polysaccharides, nucleic acids
NAD+
NADH
ADP+P
ATP
NADP+
NADPH
SIMPLE MOLECULES
e.g., CO2, H2O, urea, ammonia, amino acids, simple sugars, fatty acids, nitrogenous bases

On the left – In catabolic pathways, the oxidation of macronutrients is coupled with the reduction of NAD$^+$; NAD$^+$ accepts electrons and becomes reduced (NADH).
On the right – In anabolic pathways, the oxidation of NADPH provides electrons needed for the biosynthesis of macromolecules; NADPH donates electrons and becomes oxidized (NADP$^+$).

[Figure 4 - Click to Enlarge]

NAD as a substrate for NAD-consuming enzymes

The niacin coenzyme, NAD, is the substrate (reactant) for at least four classes of enzymes. Two classes of enzymes with mono adenosine diphosphate (ADP)-ribosyltransferase and/or poly (ADP-ribose) polymerase activities catalyze ADP-ribosyl transfer reactions. Silent information regulator-2 (Sir2)-like proteins (sirtuins) catalyze the removal of acetyl groups from acetylated proteins, utilizing ADP-ribose from NAD as an acceptor for acetyl groups. Finally, ADP-ribosylcyclases are involved in the regulation of intracellular calcium signaling.

ADP-ribosylation

Enzymes with ADP-ribosyltransferase activities were formerly divided between mono ADP-ribosyltransferases (ARTs) and poly (ADP-ribose) polymerases (PARPs). ARTs were first discovered in certain pathogenic bacteria — like those causing cholera or diphtheria — where they mediate the actions of toxins. These enzymes transfer an ADP-ribose residue moiety from NAD to a specific amino acid of a target protein, with the creation of an ADP-ribosylated protein and the release of nicotinamide.

Because most PARPs have been found to exhibit only mono ADP-ribosyltransferase activities, a new nomenclature was proposed for enzymes catalyzing ADP-ribosylation: A family of mono ADP-ribosyltransferases with homology to bacterial diphtheria toxins was named ARTD, while enzymes with either mono or poly ADP-ribosyltransferase activities and related to C2 and C3 clostridial toxins were included in the ARTC family (7, 8).

- **ARTCs** are extracellular enzymes that catalyze the mono ADP-ribosylation of membrane or secreted proteins involved in innate immunity and cell communication (2).
- **ARTDs** are intracellular enzymes with either mono or poly ADP-ribosyltransferase activities. At least 18 ARTDs have been identified. All ARTDs possess a diphtheria toxin-like catalytic domain that binds NAD$^+$. Only ARTDs 1, 2, 5, and 6 catalyze poly (ADP-ribose) transfers; the others have mono ADP-ribosyltransferase activities. ARTDs were shown to be involved in DNA repair and stress responses, cell signaling, transcription regulation, apoptosis, cell differentiation, maintenance of genomic integrity, and antiviral defense (reviewed in 8).

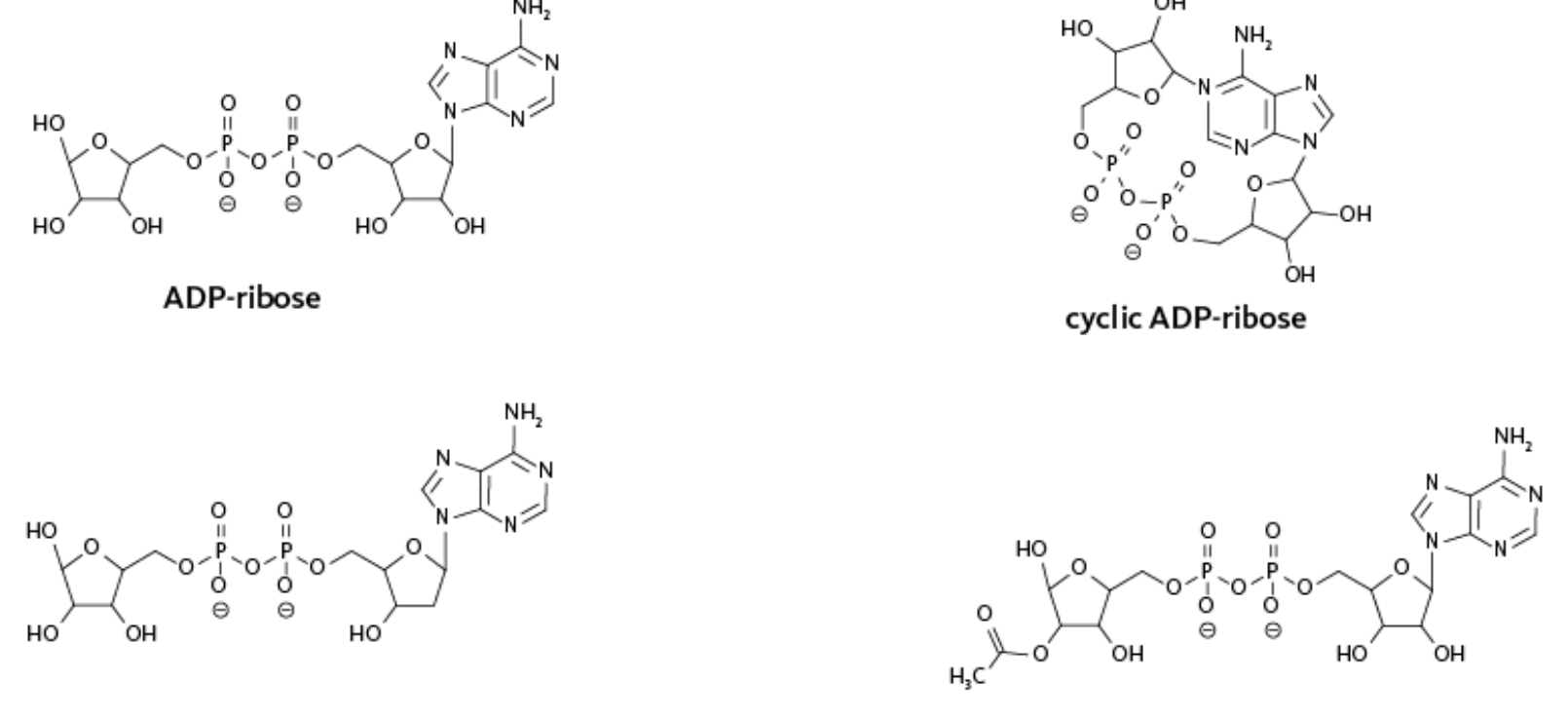
NAD-dependent deacetylation

Seven **sirtuins** (SIRT 1-7) have been identified in humans. Sirtuins are a class of NAD-dependent deacetylase enzymes that remove acetyl groups from the acetylated lysine residues of target proteins. During the deacetylation process, the acetyl group is transferred onto the ADP-ribose moiety cleaved off NAD, producing O-acetyl-ADP-ribose. Nicotinamide can exert feedback inhibition to the deacetylation reaction (9). Like ADP-ribosylation, acetylation is a post-translational modification that affects the function of target proteins. The initial interest in sirtuins followed the discovery that their activation could mimic caloric restriction, which has been shown to increase lifespan in lower organisms. Such a role in mammals is controversial, although sirtuins are energy-sensing regulators involved in signaling pathways that could play important roles in delaying the onset of age-related diseases (e.g., cardiovascular disease, cancer, dementia, arthritis). To date, the spectrum of their biological functions includes gene silencing, DNA damage repair, cell cycle regulation, and cell differentiation (10).

Calcium mobilization

In humans, CD38 and CD157 belong to a family of **NAD$^+$ glycohydrolases/ADP-ribosylcyclases**. These enzymes catalyze the formation of key regulators of calcium signaling, namely (linear) ADP-ribose, cyclic ADP-ribose, and nicotinic acid adenine dinucleotide phosphate (**Figure 5**). Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate works within cells to provoke the release of calcium ions from internal storage sites (i.e., endoplasmic reticulum, lysosomes, mitochondria), whereas ADP-ribose stimulates extracellular calcium entry through cell membrane TRPM2 cation channels (2). Another TRPM2 agonist, 2'-deoxy-ADP-ribose, was recently identified *in vitro*. CD38 was found to catalyze the synthesis of 2'-deoxy-ADP-ribose from nicotinamide mononucleotide and 2'-deoxy-ATP (11). *O*-acetyl-ADP-ribose generated by the activity of sirtuins also controls calcium entry through TRPM2 channels (6). Intracellular calcium-mediated signal transduction is regulated by transient calcium entry into the cell or release of calcium from intracellular stores. Calcium signaling is critically involved in processes like neurotransmission, insulin release from pancreatic β-cells, muscle cell contraction, and T-lymphocyte activation (6).

Figure 5. Calcium-mobilizing Derivatives of Niacin



[Figure 5 - Click to Enlarge]

NAD as a ligand

NAD^+ has been identified as an endogenous agonist of purinergic membrane receptors of the P2Y subclass. In particular, NAD was found to bind to P2Y1 receptor and act as an inhibitory neurotransmitter at neuromuscular junctions in visceral smooth muscles (12). Extracellular NAD^+ was also found to behave like a proinflammatory cytokine, triggering the activation of isolated granulocytes. NAD^+ binding to the P2Y11 receptor at the granulocyte surface activated a signaling cascade involving cyclic ADP-ribose and the rise of intracellular calcium, eventually stimulating superoxide generation and chemotaxis (13). Similar observations were made with lipopolysaccharide-activated monocytes (14). Extracellular $NAADP^+$ and ADP-ribose might also bind to P2Y receptors and trigger intracellular $NAADP^+$- and ADP-ribose-dependent calcium mobilization (see Calcium mobilization) (15, 16).

Lipid-lowering effects with pharmacologic doses of nicotinic acid

For over half a century, pharmacologic doses of nicotinic acid, but not nicotinamide, have been known to reduce serum cholesterol (see Disease Treatment) (17). However, the exact mechanisms underlying the lipid-lowering effect of nicotinic acid remain speculative. Two G-protein-coupled membrane receptors, GPR109A and GPR109B, bind nicotinic acid with high and low affinity, respectively. These nicotinic acid receptors are primarily expressed in adipose tissue and immune cells (but not lymphocytes). They are also found in retinal pigmented and colonic epithelial cells, keratinocytes, breast cells, microglia, and possibly at low levels in the liver (18). Thus, lipid-modifying effects of nicotinic acid are likely to be mediated by receptor-independent mechanisms in major tissues of lipid metabolism like liver and skeletal muscle. Early *in vitro* data suggested that nicotinic acid could impair very-low-density lipoprotein (VLDL) secretion by inhibiting triglyceride synthesis and triggering ApoB lipoprotein degradation in hepatocytes (19). In another study, nicotinic acid affected the hepatic uptake of ApoAI lipoprotein, thereby reducing high-density lipoprotein (HDL) removal from the circulation (reviewed in 20). In adipocytes, the binding of nicotinic acid to GPR109A was found to initiate a signal transduction cascade resulting in reductions in free fatty acid production via the inhibition of hormone-sensitive lipase involved in triglyceride lipolysis (21). Nonetheless, recent observations have suggested that the lipid-lowering effect of nicotinic acid was not due to its anti-lipolytic activity (22). Trials showed that synthetic agonists of GPR109A acutely lowered free fatty acids yet failed to affect serum lipids (22). Aside from its impact on HDL and other plasma lipids, nicotinic acid has exhibited anti-atherosclerotic activities in cultured monocytes, macrophages, or vascular endothelial cells, by modulating inflammation and oxidative stress and regulating cell adhesion, migration, and differentiation (reviewed in 18).

Deficiency

Pellagra

Causes

The late stage of severe niacin deficiency is known as pellagra. Early records of pellagra followed the widespread cultivation of corn in Europe in the 1700s (23). The disease is generally associated with poorer social classes whose chief dietary staple consisted of cereal like corn or sorghum. Pellagra was also common in the southern United States during the early 1900s where income was low and corn products were a major dietary staple (24). Interestingly, pellagra was not known in Mexico, where corn was also an important dietary staple and much of the population was also poor. In fact, if corn contains appreciable amounts of niacin, it is present in a bound form that is not nutritionally available to humans. The traditional preparation of corn tortillas in Mexico involves soaking the corn in a lime (calcium oxide) solution, prior to cooking. Heating the corn in an alkaline solution results in the release of bound niacin, increasing its bioavailability (25). Pellagra epidemics were also unknown to Native Americans who consumed immature corn that contains predominantly unbound (bioavailable) niacin (24).

Niacin deficiency or pellagra may result from inadequate dietary intake of NAD precursors, including tryptophan. Niacin deficiency — often associated with malnutrition — is observed in the homeless population, in individuals suffering from anorexia nervosa or obesity, and in consumers of diets high in maize and poor in animal protein (26-29). Deficiencies of other B vitamins and some trace minerals may aggravate niacin deficiency (30, 31). Malabsorptive disorders that can lead to pellagra include Crohn's disease and megaduodenum (32, 33). Patients with Hartnup's disease, a hereditary disorder resulting in defective tryptophan absorption, have developed pellagra (see Niacin-responsive genetic disorders). Carcinoid syndrome, a condition of increased secretion of serotonin and other catecholamines by carcinoid tumors, may also result in pellagra due to increased utilization of dietary tryptophan for serotonin rather than niacin synthesis. Further, prolonged treatment with the anti-tuberculosis drug isoniazid has resulted in niacin deficiency (34). Other pharmaceutical agents, including the immunosuppressive drugs azathioprine (Imuran) and 6-mercaptopurine, the anti-cancer drug 5-fluorouracil (5-FU, Adrucil), and levodopa/carbidopa (Sinemet; two drugs given to people with Parkinson's disease), are known to increase the reliance on dietary niacin by interfering with the tryptophan-kynurenine-niacin pathway (35). Finally, other populations at risk for niacin deficiency include dialysis patients, cancer patients (36, 37), individuals suffering from chronic alcoholism (38), and people with HIV (see HIV/AIDS below). Further, chronic alcohol intake can lead to severe niacin deficiency through reducing dietary niacin intake and interfering with the tryptophan-to-NAD conversion (30).

Symptoms of deficiency

The most common symptoms of niacin deficiency involve the skin, the digestive system, and the nervous system. The symptoms of pellagra are commonly referred to as the three "Ds": sun-sensitive dermatitis, diarrhea, and dementia. A fourth "D," death, occurs if pellagra is left untreated (5). In the skin, a thick, scaly, darkly pigmented rash develops symmetrically in areas exposed to sunlight. In fact, the word "pellagra" comes from "*pelle agra*," the Italian phrase for rough skin. Symptoms related to the digestive system include inflammation of the mouth and tongue ("bright red tongue"), vomiting, constipation, abdominal pain, and ultimately, diarrhea. Gastrointestinal disorders and diarrhea contribute to the ongoing malnourishment of the patients. Neurologic symptoms include headache, apathy, fatigue, depression, disorientation, and memory loss and are more consistent with delirium than with the historically described dementia (38). Disease presentations vary in appearance since the classic triad rarely presents in its entirety. The absence of dermatitis, for example, is known as pellagra *sine* pellagra.

Treatment

To treat pellagra, the World Health Organization (WHO) recommends administering nicotinamide to avoid the flushing commonly caused by nicotinic acid (see Safety). Treatment guidelines suggest using 300 mg/day of oral nicotinamide in divided doses, or 100 mg/day administered parenterally in divided doses, for three to four weeks (37, 39). Because patients with pellagra often display additional vitamin deficiencies, administration of a vitamin B-complex preparation is advised (39).

The Recommended Dietary Allowance (RDA)

Niacin equivalent (NE)

The term "niacin equivalent" (NE) is used to describe the contribution to dietary intake of all the forms of niacin that are available to the body. In healthy individuals, less than 2% of dietary tryptophan is converted to NAD in the kynurenine pathway (40). The synthesis of NAD from tryptophan is fairly inefficient and depends on enzymes requiring vitamin B_6 and riboflavin, as well as a heme (iron)-containing enzyme. Nonetheless, tryptophan is essential as a precursor for NAD^+. Inherited defects in tryptophan transport and metabolism result in severe clinical disorders attributed to NAD^+ depletion (see Niacin-responsive genetic disorders). On average, 60 milligrams (mg) of tryptophan are considered to correspond to 1 mg of niacin or 1 mg of NE.

Daily recommended intakes

The recommended dietary allowance (RDA) for niacin is based on the prevention of deficiency. Pellagra can be prevented by about 11 mg NE/day, but 12 mg to 16 mg NE/day has been found to normalize the urinary excretion of niacin metabolites (breakdown products) in healthy young adults. Because pellagra represents severe deficiency, the Food and Nutrition Board (FNB) of the US Institute of Medicine chose to use the excretion of niacin metabolites as an indicator of niacin nutritional status rather than symptoms of pellagra (41). However, it has been argued that cellular NAD and NADP content may be more relevant indicators of niacin nutritional status (24).

Table 1. Recommended Dietary Allowance (RDA) for Niacin

Life Stage	Age	Males (mg NE*/day)	Females (mg NE/day)
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	4 (AI)	4 (AI)
Children	1-3 years	6	6
Children	4-8 years	8	8
Children	9-13 years	12	12
Adolescents	14-18 years	16	14
Adults	19 years and older	16	14
Pregnancy	all ages	-	18
Breast-feeding	all ages	-	17
*NE, niacin equivalent: 1 mg NE = 60 mg of tryptophan = 1 mg niacin			

Disease Prevention

Cancer

Studies of cultured cells (*in vitro*) provide evidence that NAD content influences mechanisms that maintain genomic stability. Loss of genomic stability, characterized by a high rate of damage to DNA and chromosomes, is a hallmark of cancer (42). The current understanding is that the pool of NAD is decreased during niacin deficiency and that it affects the activity of NAD-consuming enzymes rather than redox and metabolic functions (43). Among NAD-dependent reactions, poly ADP-ribosylations catalyzed by PARP enzymes (ARTDs) are critical for the cellular response to DNA injury. After DNA damage, PARPs are activated; the subsequent poly ADP-ribosylations of a number of signaling and structural molecules by PARPs were shown to facilitate DNA repair at DNA strand breaks (44). Cellular depletion of NAD has been found to decrease levels of the tumor suppressor protein p53, a target for poly ADP-ribosylation, in human breast, skin, and lung cells (45). The expression of p53 was also altered by niacin deficiency in rat bone marrow cells (46). Impairment of DNA repair caused by niacin deficiency could lead to genomic instability and drive tumor development in rat models (47, 48). Both PARPs and sirtuins have been recently involved in the maintenance of heterochromatin, a chromosomal domain associated with genome stability, as well as in transcriptional gene silencing, telomere integrity, and chromosome segregation during cell division (49, 50). Neither the cellular NAD content nor the dietary intake of NAD precursors necessary for optimizing protective responses following DNA damage has been determined, but both are likely to be higher than that required for the prevention of pellagra.

Bone marrow

Cancer patients often suffer from bone marrow suppression following chemotherapy, given that bone marrow is one of the most proliferative tissues in the body and thus a primary target for chemotherapeutic agents. Niacin deficiency was found to decrease bone marrow NAD and poly-ADP-ribose levels and increase the risk of chemically induced leukemia in rats (51). Conversely, a pharmacologic dose of either nicotinic acid or nicotinamide was able to increase NAD and poly ADP-ribose in bone marrow and decrease the development of leukemia in rats (52). It has been suggested that niacin deficiency often observed in cancer patients could sensitize bone marrow tissue to the suppressive effect of chemotherapy. However, little is known regarding cellular NAD levels and the prevention of DNA damage or cancer in humans. One study in two healthy individuals involved elevating NAD levels in blood lymphocytes by supplementation with 100 mg/day of nicotinic acid for eight weeks. Compared to non-supplemented individuals, the supplemented individuals had reduced DNA strand breaks in lymphocytes exposed to free radicals in a test tube assay (53). However, nicotinic acid supplementation of up to 100 mg/day for 14 weeks in 21 healthy smokers failed to provide any evidence of a decrease in cigarette smoke-induced genetic damage in blood lymphocytes compared to placebo (54). More recently, the frequency of chromosome translocation was used to evaluate DNA damage in peripheral blood lymphocytes of 82 pilots chronically exposed to ionizing radiation, a known human carcinogen. In this observational study, the rate of chromosome aberrations was significantly lower in subjects with higher (28.4 mg/day) compared to lower (20.5 mg/day) dietary niacin intake (55). Higher availability of NAD^+ in X-irradiated peripheral blood lymphocytes was found to favor DNA repair by enhancing survival, particularly through SIRT-mediated p53 deacetylation (56).

Upper digestive tract

Generally, relationships between dietary factors and cancer are established first in epidemiological studies and followed up by basic cancer research at the cellular level. In the case of niacin, research on biochemical and cellular aspects of DNA repair has stimulated an interest in the relationship between niacin intake and cancer risk in human populations (57). A large case-control study found increased consumption of niacin, along with antioxidant nutrients, to be associated with decreased incidence of oral (mouth), pharyngeal (throat), and esophageal cancers in northern Italy and Switzerland. An increase in daily niacin intake of 6.2 mg was associated with about a 40% decrease in cases of cancers of the mouth and throat, while a 5.2 mg increase in daily niacin intake was associated with a similar decrease in cases of esophageal cancer (58, 59).

Skin

Niacin deficiency can lead to severe sunlight sensitivity in exposed skin. Given the implication of NAD-dependent enzymes in DNA repair, there has been some interest in the effect of niacin on skin health. *In vitro* and animal experiments have helped gather information, but human data on niacin/NAD status and skin cancer are very limited. One study reported that niacin supplementation decreased the risk of ultraviolet light (UV)-induced skin cancers in mice, despite the fact that mice convert tryptophan to NAD more efficiently than rats and humans and thus do not get severely deficient (60). Hyper-proliferation and impaired differentiation of skin cells can alter the integrity of the skin barrier and increase the occurrence of pre-malignant and malignant skin conditions. A protective effect of niacin was suggested by topical application of myristyl nicotinate, a niacin derivative, which successfully increased the expression of epidermal differentiation markers in subjects with photodamaged skin (61). The activation of the nicotinic acid receptors, GPR109A and GPR109B, by pharmacologic doses of niacin could be involved in improving skin barrier function. Conversely, differentiation defects in skin cancer cells were linked to the abnormal cellular localization of defective nicotinic acid receptors (62). Nicotinamide restriction with subsequent depletion of cellular NAD was shown to increase oxidative stress-induced DNA damage in a precancerous skin cell model, implying a protective role of NAD-dependent pathways in cancer (63). Altered NAD availability also affects sirtuin expression and activity in UV-exposed human skin cells. Along with PARPs, NAD-consuming sirtuins could play an important role in the cellular response to photodamage and skin homeostasis (64).

A pooled analysis of two large US prospective cohort studies that followed 41,808 men and 72,308 women for up to 26 years suggested that higher versus lower intake of niacin (from diet and supplements) might be protective against squamous-cell carcinoma but not against basal-cell carcinoma and melanoma (65). A phase III, randomized, double-blind, placebo-controlled trial in 386 subjects with a history of nonmelanoma skin cancer recently examined the effect of daily nicotinamide supplementation (1 g) for 12 months on skin cancer recurrence at three-month intervals over an 18-month period (66). Nicotinamide effectively reduced the rate of premalignant actinic keratose (-11%), squamous-cell carcinoma (-30%), and basal-cell carcinoma (-20%) compared to placebo after 12 months, yet this protection was not sustained during the six-month post-supplementation period (66). Larger trials are needed to assess whether nicotinamide could reduce the risk of melanomas, which are not as common as other skin cancer but are more deadly (67).

Type 1 diabetes mellitus

Type 1 diabetes mellitus in children is caused by the autoimmune destruction of insulin-secreting β-cells in the pancreas. Prior to the onset of symptomatic diabetes, specific antibodies, including islet cell autoantibodies (ICA), can be detected in the blood of high-risk individuals (68). In an experimental animal model of diabetes, high levels of nicotinamide are administered to protect β-cells from damage caused by streptozotocin (69).

Yet, pharmacologic doses of nicotinamide (up to 3 g/day) have not been found to be effective in delaying or preventing the onset of type 1 diabetes in at-risk subjects. An analysis of 10 trials, of which five were placebo-controlled, found evidence of improved β-cell function after one year of treatment with nicotinamide, but the analysis failed to find any clinical evidence of improved glycemic control (70). A large, multicenter randomized controlled trial of nicotinamide in ICA-positive siblings (ages, 3-12 years) of type 1 diabetic patients also failed to find a difference in the incidence of type 1 diabetes after three years (70). A randomized, double-blind, placebo-controlled multicenter trial of nicotinamide (maximum of 3 g/day) was conducted in 552 ICA-positive relatives of patients with type 1 diabetes. The proportion of relatives who developed type 1 diabetes within five years was comparable whether they were treated with nicotinamide or placebo (71). Nicotinamide could reduce inflammation-related parameters in these high-risk subjects yet was ineffective to prevent disease onset (72). More recently, case reports of the combined use of nicotinamide (25 mg/kg/day) and acetyl-L-carnitine (50 mg/kg/day) in children at risk for type 1 diabetes showed promising results, warranting further investigation (73).

Disease Treatment

Niacin supplements at pharmacologic doses (i.e., doses much larger than those needed to prevent deficiency) have been used in an attempt to treat a range of conditions, some of which are discussed below.

Niacin-responsive genetic disorders

Congenital NAD deficiency-related disorders can result from mutations in genes involved in the uptake and transport of the various dietary NAD^+ precursors or in the distinct metabolic pathways leading to NAD^+ production (see Metabolism). Some of these disorders might respond to niacin supplementation. For example, defective transport of tryptophan into cells results in Hartnup disease, which features signs of severe niacin deficiency (74). Hartnup disease is due to mutations in the *SLCA19* gene, which codes for a sodium-dependent neutral amino acid transporter expressed primarily in the kidneys and intestine. Disease management involves supplementation with nicotinic acid or nicotinamide (75). Recessive mutations in genes coding for enzymes of the kynurenine pathway — namely kynureninase and 3-hydroxyanthranilic-acid 3,4-dioxygenase — lead to combined vertebral, anal, cardiac, tracheo-esophageal, renal, and limb (VACTERL) congenital malformations (76). Depletion of NAD^+, rather than accumulation of intermediate metabolites in the kynurenine pathway, was found to be responsible for these malformations. Niacin supplementation throughout pregnancy ensured adequate levels of NAD^+ and prevented congenital anomalies in mice with kynurenine pathway mutations (76). In humans, the dose of NAD^+ precursors necessary to avert NAD deficiency-induced congenital VACTERL malformations has yet to be defined (77).

Nicotinamide may also rescue NAD^+ depletion secondary to an ultra-rare inborn error of glutamine metabolism (78). Glutamine is required for the conversion of nicotinic acid adenine dinucleotide to NAD^+ catalyzed by NAD^+ synthetase (**Figure 2**). Thus, inherited glutamine synthetase deficiency specifically affects the synthesis of NAD^+ from the NAD^+ precursors, tryptophan and nicotinic acid. If the combined deficiencies of glutamine and NAD^+ are responsible for the severe clinical phenotype of subjects with inherited glutamine synthetase deficiency, it is likely that supplementation with both glutamine and nicotinamide would provide some relief (78).

Finally, many inborn errors of metabolism result from genetic mutations decreasing cofactor binding affinity and, subsequently, enzyme efficiency (79). In many cases, the administration of high doses of the vitamins serving as precursors of cofactors can restore enzymatic activity — at least partially — and lessen signs of the genetic diseases (79). Given the large number of enzymes requiring NAD, it is speculated that many of the conditions due to defective enzymes might be rescued by niacin supplementation (5).

Cardiovascular disease

Cardiovascular risk factors

Nicotinic acid is a well-known lipid-lowering agent: Nicotinic acid therapy markedly increases high-density lipoprotein (HDL) cholesterol concentrations, decreases serum lipoprotein(a) concentrations, and shifts small, dense low-density lipoprotein (LDL) particles to large, buoyant LDL particles. All of these changes in the blood lipid profile are considered cardioprotective. Low concentrations of HDL-cholesterol are one major risk factor for coronary heart disease (CHD), and an increase in HDL concentrations is associated with a reduction of that risk (80). Because of the adverse side effects associated with high doses of nicotinic acid (see Safety), nicotinic acid has most often been used in combination with other lipid-lowering medications at slightly lower doses (17). In particular, low-dose nicotinic acid is often co-administered with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), the cornerstone of treatment of hyperlipidemia, a major risk factor for CHD. A placebo-controlled study in 39 patients taking statins (cerivastatin, atorvastatin, or simvastatin) found that a very low dose of nicotinic acid (100 mg/day) increased HDL-cholesterol by only 2.1 mg/dL, and the combination had no effect on LDL-cholesterol, total cholesterol, or triglyceride concentrations (81).

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study — a double-blind, placebo-controlled trial — investigated the incremental effect of adding nicotinic acid (1 g/day) to statin therapy in 167 patients with known CHD and low HDL concentrations on carotid intima-media thickness (CIMT) (82), a surrogate endpoint for the development of atherosclerosis. The addition of extended-release nicotinic acid to simvastatin prevented the increase in CIMT compared to simvastatin monotherapy. A post-hoc analysis of data from ARBITER2 showed that the blockade of atherosclerotic progression was related to the increase in HDL concentrations in patients with normal glycemic status. However, in the presence of additional risk factors, such as impaired fasting glucose or diabetes mellitus, the increase in HDL concentrations was not predictive of CIMT reduction and atherosclerotic retardation (83). A comparative efficacy trial (ARBITER6) also showed a significant reduction of baseline CIMT with extended-release nicotinic acid (2 g/day for 14 months), as opposed to ezetimibe (a cholesterol-lowering drug), in patients taking statins (84).

Additional studies have examined the impact of nicotinic acid on endothelium-dependent brachial flow-mediated dilation (FMD) in patients at risk of CHD or with established CHD. The measurement of FMD is often used as a surrogate marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (85). A meta-analysis of seven randomized controlled trials, including 441 participants, showed a significant, 2% increase with nicotinic acid (1-2 g/day) administered for 12 weeks to one year (86).

Cardiovascular events

Several randomized, placebo-controlled, multicenter trials have investigated the efficacy and safety of nicotinic acid therapy, alone or in combination with other lipid-lowering agents, on outcomes of cardiovascular disease (CVD). Specifically, the Coronary Drug Project (CDP) followed over 8,000 men with a previous myocardial infarction for six years (87). Compared to the placebo group, patients who took 3 g of immediate-release nicotinic acid daily experienced an average 10% reduction in total blood cholesterol, a 26% decrease in triglycerides, a 27% reduction in recurrent nonfatal myocardial infarction, and a 26% reduction in cerebrovascular events (stroke and transient ischemic attacks). In addition, nine-year follow-up post-trial revealed a 10% reduction in total deaths with nicotinic acid treatment.

The HDL-Atherosclerosis Treatment Study (HATS), a three-year randomized controlled trial in 160 patients with documented CHD and low HDL concentrations, found that a combination of simvastatin and nicotinic acid (2-3 g/day) increased HDL concentrations, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, including myocardial infarction and stroke, compared to placebo (88). A subgroup analysis of the HATS patients with metabolic syndrome showed a reduction in rate of primary clinical events even though glucose and insulin metabolism were moderately impaired by nicotinic acid (89). Moreover, a review of nicotinic acid safety and tolerability among the HATS subjects showed glycemic control in diabetic patients returned to pretreatment values following eight months of disease management with medication and diet (90). Similarly, the cardiovascular benefit of long-term nicotinic acid therapy outweighed the modest increase in risk of newly onset type 2 diabetes in patients from the CDP study (91).

In contrast, the AIM-HIGH (Atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on global health outcomes) trial, which examined the incremental effect of extended-release nicotinic acid (1.5-2 g/day) on 3,414 patients who had established CVD and atherogenic dyslipidemia and were treated with simvastatin (+/- ezetimibe), provided disappointing results. Indeed, in these patients who had achieved target concentrations of LDL-cholesterol (<70 mg/dL) before randomization, the HDL-raising effect of nicotinic acid treatment failed to reduce the number of cardiovascular events after a mean follow-up of three years (92, 93). While some limitations, like a greater use of simvastatin and ezetimibe in the control group, may have confounded the results, it was also suggested that low HDL-cholesterol might be a marker of risk rather than a causal risk factor for predicting CVD (93). In addition, a post-hoc analysis of 505 participants with stage 3 chronic kidney disease found an increase in all-cause mortality in those randomized to nicotinic acid compared to those in the placebo group (94).

Although nicotinic acid failed to reduce the number of cardiovascular events in simvastatin-treated patients with low LDL-cholesterol, these results cannot be extrapolated to patients with higher LDL-cholesterol at baseline. A much larger multicenter, randomized, double-blind, placebo-controlled trial — the HPS2-THRIVE (Heart protection study 2: treatment of HDL to reduce the incidence of vascular events) trial — in 25,673 participants with vascular disease examined the incremental effect of extended-release nicotinic acid (2 g/day) and laropiprant (a prostaglandin D2 receptor-1 antagonist; 40 mg/day) on the incidence of vascular events. Compared to placebo, nicotinic acid/laropiprant reduced LDL-cholesterol by an average of 10 mg/dL, decreased triglycerides by 33 mg/dL, and increased HDL-cholesterol by 6 mg/dL after a median 3.9-year follow-up period. Nonetheless, nicotinic acid/laropiprant showed no effect on the incidence of major vascular events and death of any cause (95).

A recent meta-analysis of 23 randomized controlled trials — including the CDP, AIM-HIGH, and HPS2-THRIVE trials — in 39,195 subjects with a history of vascular disease compared the effect of nicotinic acid alone or as an add-on to other lipid-lowering agents. No cardiovascular benefits were associated with nicotinic acid therapy: the number of fatal and non-fatal myocardial infarctions and strokes was not decreased with nicotinic acid supplementation (median dose of 2 g/day for a median period of 11.5 months) (96).

Despite the lack of evidence for a role of nicotinic acid in CVD prevention (96, 97), the use of nicotinic acid therapy has rapidly increased over the years in the US (98).

Friedreich's ataxia

Friedreich's ataxia, a common form of inherited ataxia, is an early onset recessive disorder with clinical features that includes progressive ataxia, scoliosis, dysarthria, cardiomyopathy, and diabetes mellitus (99). Most affected subjects carry homozygous guanine-adenine-adenine (GAA) repeat expansions in the first intron of the gene *FXN* coding for the protein frataxin. These abnormal and unstable GAA repeats trigger gene silencing through heterochromatin formation, leading to significantly reduced frataxin expression (100). Frataxin is a mitochondrial protein needed for the making of iron-sulfur clusters (ISC). ISC-containing subunits are especially important for the mitochondrial respiratory chain and for the synthesis of heme-containing proteins (99).

Predominantly localized in the nucleus, SIRT1 is a NAD^+-dependent deacetylase that promotes gene silencing through heterochromatin formation. Nicotinamide has been shown to antagonize heterochromatization of the *FXN* locus and upregulate frataxin expression in lymphoblastoid cells derived from Friedreich's ataxia-affected patients, possibly through inhibiting SIRT1 activity (100). In an open-label, dose escalating pilot trial in 10 adult patients with Friedreich's ataxia, single and repeated doses of nicotinamide (2-8 g) for up to eight weeks were found to be well tolerated (101). Repeated daily doses of 3.5 to 6 g of nicotinamide led to significant increases in frataxin concentration in peripheral white blood cells (101). Yet, no neurological improvements were reported, suggesting that the duration of the treatment was too short and/or the nervous system of the participants was unresponsive to increases in frataxin (102). To our knowledge, there is currently no ongoing trial designed to further investigate the effect of nicotinamide in Friedreich's ataxia-affected patients.

HIV/AIDS

The first step in the kynurenine pathway is catalyzed by the extrahepatic enzyme, indoleamine 2,3-dioxygenase (IDO), which is responsible for the oxidative cleavage of tryptophan. The chronic stimulation of tryptophan oxidation, mediated by an increased activity of IDO and/or inadequate dietary niacin intakes, is observed with the infection of human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS). Interferon-gamma (IFN-γ) is a cytokine produced by cells of the immune system in response to infection. Through stimulating the enzyme IDO, IFN-γ increases the breakdown of tryptophan, thus supporting the finding that the average tryptophan concentration in blood is significantly lower in HIV patients compared to uninfected subjects (40). An increased degradation of tryptophan via the kynurenine pathway appears to coexist with intracellular niacin/NAD deficiency in HIV infection (103). An explanatory model for these paradoxical observations incriminates the oxidative stress induced by multiple nutrient deficiencies in HIV patients (103). In particular, the activation of PARP enzymes (ARTDs) by oxidative damage to DNA could be responsible for inducing niacin/NAD depletion (see Function). The breakdown of tryptophan would then be a compensatory response to inadequate niacin/NAD levels.

However, metabolites derived from the oxidation of tryptophan in the kynurenine pathway regulate specific T-lymphocyte subgroups. As mentioned above, circulating IFN-γ, but also viral and bacterial products, can activate IDO during HIV infection. The overstimulation of the tryptophan pathway has been involved in the loss of normal T-lymphocyte function, which characterizes HIV infection (104, 105). The increased IDO activity has been linked to the altered immune response that contributes to the persistence of HIV (104). Antiretroviral therapy (ART) only partially restores normal IDO activity, without normalizing it, yet induces viral suppression and CD4 T-cell recovery (106). In a monkey model for HIV infection, a partial and transient blockade of IDO with IDO inhibitor 1-methyl tryptophan proved ineffective to reduce the viral load in plasma and intestinal tissues beyond the level achieved by ART (107). At present, a better understanding of the role of kynurenine pathway and other NAD biosynthetic pathways during HIV infection is needed before the relevance and clinical implications of niacin supplementation in HIV treatment could be considered.

Nonetheless, pharmacologic doses of nicotinic acid have been shown to be well tolerated in HIV patients with hyperlipidemia (108). Abnormal lipid profiles observed in patients have been attributed to the HIV infection and to the highly active antiretroviral treatment (HAART) (109). Moreover, insulin resistance has been detected together with dyslipidemia in ART-treated patients (110). Cardiovascular disease (CVD) is the second most frequent cause of deaths in the HIV population, and the rate of CVD is predicted to increase further as patients are living longer due to successful antiretroviral therapies. As for the general population, statin-based therapy appears to benefit HIV patients in terms of atherogenic protection and CVD risk reduction, although contraindications exist due to drug interactions with ART. Other first-line treatments include lipid-lowering fibrates, which are preferred to nicotinic acid due to the increased risk of glucose intolerance and insulin resistance (111). Nevertheless, an unblinded, controlled pilot study showed that extended-release nicotinic acid (0.5-1.5 g/day for 12 weeks) could effectively improve endothelial function of the brachial artery in ART-treated HIV subjects with low HDL-cholesterol and no history of CVD (112). In addition, a combined treatment of fibrates, extended-release nicotinic acid (0.5-2 g/day), and lifestyle changes (low-fat diet and exercise) for 24 weeks was effective in normalizing lipid parameters in a cohort of 191 ART-treated patients. Increased risk of liver dysfunction was detected in subjects receiving both fibrates and niacin, but insulin sensitivity was not affected by nicotinic acid treatment given alone or when combined with fibrates (113). Another 24-week, open-label, uncontrolled trial in 99 ART-treated patients found that randomization to extended-release nicotinic acid (0.5-2 g/day) or fenofibrates increased blood HDL-cholesterol but did not reduce inflammatory markers or improve endothelial function when compared to baseline (114).

Schizophrenia

Schizophrenia is a neurologic disorder with unclear etiology that is diagnosed purely from its clinical presentation. Because neurologic disorders associated with pellagra resemble acute schizophrenia, niacin-based therapy for the condition was investigated during the 1950s-70s (reviewed in 115). The adjunctive use of nutrients like niacin to correct deficiencies associated with neurologic symptoms is called orthomolecular psychiatry (116). Such an approach has not been included in psychiatric practice; practitioners have instead relied solely on antipsychotic drugs to eliminate the clinical symptoms of schizophrenia. Nevertheless, recent scientific advances and new hypotheses on the benefit of nutrient supplementation in the treatment of psychiatric disorders have suggested the re-assessment of orthomolecular medicine by the medical community (117, 118).

Skin flushing is one major side effect of the therapeutic use of nicotinic acid and the primary reason for non-adherence to treatment (see Toxicity). Flushing is caused by the activation of phospholipase A2, an enzyme that stimulates the production of a specific lipid from the prostanoid family called prostaglandin D2. Prostaglandin D2, synthesized by antigen-presenting cells of the skin and mucosa (i.e., the Langerhans cells), can induce the dilation of blood vessels and trigger a flushing response. Interestingly, patients with schizophrenia tend not to flush following treatment with nicotinic acid. This blunted skin flushing response suggests abnormal prostanoid signaling in schizophrenic patients (119, 120). An association has been found between the altered niacin sensitivity and greater functional impairment in schizophrenic subjects (121), which supports other findings suggesting that altered lipid metabolism could critically impair brain development and contribute to the disease (122). Interestingly, blunted skin flushing responses are more prevalent in first-degree relatives of people with schizophrenia than in the general population, suggesting that reduced niacin sensitivity is a heritable trait within affected families (123).

Sources

Food sources

Good sources of niacin include yeast, meat, poultry, red fish (e.g., tuna, salmon), cereal (especially fortified cereal), legumes, and seeds. Milk, green leafy vegetables, coffee, and tea also provide some niacin (124). In plants, especially mature cereal grains like corn and wheat, niacin may be bound to sugar molecules in the form of glycosides, which significantly decrease its bioavailability (25).

In the United States, the average dietary intake of niacin is about 30 mg/day for young adult men and 20 mg/day for young adult women. In a sample of adults over the age of 60, men and women were found to have an average dietary intake of 21 mg/day and 17 mg/day, respectively (41). Some foods with substantial amounts of niacin are listed in **Table 2**, along with their niacin content in milligrams (mg). Food composition tables generally list niacin content without including niacin equivalents (NE) from tryptophan or any adjustment for niacin bioavailability. For more information on the nutrient content of specific foods, search USDA's FoodData Central database; data included in **Table 2** are from this database (125).

Table 2. Some Food Sources of Niacin

Food	Serving	Niacin (mg)
Chicken (light meat, cooked without skin)	3 ounces*	8.9
Tuna (light, canned, packed in water)	3 ounces	8.6
Turkey (light meat, cooked without skin)	3 ounces	9.9
Salmon (chinook, cooked)	3 ounces	8.5
Beef (90% lean, cooked)	3 ounces	4.4
Cereal (unfortified)	1 cup	5-7
Cereal (fortified)	1 cup	20-27
Peanuts (dry-roasted)	1 ounce	4.1
Pasta (enriched, cooked)	1 cup	1.9-2.4
Lentils (cooked)	1 cup	2.1
Lima beans (cooked)	1 cup	0.8
Bread (whole-wheat)	1 slice	1.4
Coffee (brewed)	1 cup	2
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

Niacin supplements are available as nicotinamide or nicotinic acid. Nicotinamide is the form of niacin typically used in nutritional supplements and in food fortification. Nicotinic acid is available over the counter and with a prescription as a cholesterol-lowering agent (126). Nicotinic acid for anti-hyperlipidemic use is available in three formulations: immediate-release (crystalline) nicotinic acid (absorption time, 1-2 hrs), extended-release nicotinic acid (absorption time, 8-12 hrs), and sustained-release nicotinic acid (absorption time, >12 hrs) (127). At the pharmacologic dose required for cholesterol-lowering effects, the use of nicotinic acid should be approached as if it were a drug (see Safety). Individuals should only undertake cholesterol-lowering therapy with nicotinic acid under the supervision of a qualified health care provider in order to minimize potentially adverse effects and maximize therapeutic benefits.

Safety

Toxicity

Nicotinic acid

Common side effects of nicotinic acid include flushing, pruritus (severe itching of the skin), skin rashes, and gastrointestinal disturbances, such as nausea and vomiting (97). Transient episodes of low blood pressure (hypotension) and headache have also been reported. Hepatotoxicity (liver cell damage), including elevated liver enzymes and jaundice, has been observed at intakes as low as 750 mg/day of nicotinic acid (128). Although hepatitis has been observed with extended-release nicotinic acid at dosages as little as 500 mg/day for two months, almost all reports of severe hepatitis have been associated with doses of 3 to 9 g/day used to treat high cholesterol for months or years (41). It is unclear whether immediate-release (crystalline) nicotinic acid is less toxic to the liver than extended-release forms (41). Yet, immediate-release nicotinic acid is often used at higher doses than extended-release forms, and severe liver toxicity has occurred in individuals who substituted extended-release nicotinic acid for immediate-release nicotinic acid at equivalent doses (126). Large doses of nicotinic acid have been observed to impair glucose tolerance, likely because of a decrease in insulin sensitivity. Impaired glucose tolerance in susceptible (pre-diabetic) individuals could result in elevated blood glucose concentrations and clinical type 2 diabetes mellitus. An analysis of the HPS2-THRIVE trial (see Cardiovascular disease), using data from 17,374 participants without type 2 diabetes at baseline, found a significantly higher proportion of newly diagnosed cases among those randomized to nicotinic acid/laropiprant than to placebo (5.7% versus 4.3%) over a 3.9 year-period (95). Likewise, randomization to nicotinic acid/laropiprant significantly increased the risk of serious disturbances in diabetes control (leading to hospitalization) compared to placebo among 8,299 participants with diabetes at baseline (95). Elevated blood concentrations of uric acid, occasionally resulting in attacks of gout in susceptible individuals, have also been observed with high-dose nicotinic acid therapy (126). Niacin at doses of 1.5 to 5 g/day has resulted in a few case reports of blurred vision and other eye problems, which have generally been reversible upon discontinuation (41). People with abnormal liver function or a history of liver disease, diabetes, active peptic ulcer disease, gout, cardiac arrhythmias, inflammatory bowel disease, migraine headaches, or alcoholism may be more susceptible to the adverse effects of excess niacin intake than the general population (41).

Nicotinamide

Nicotinamide is generally better tolerated than nicotinic acid; it does not generally cause flushing (126). However, nausea, vomiting, and signs of liver toxicity (elevated liver enzymes, jaundice) have been observed at very high doses (≥10 g/day) (126).

Nicotinamide riboside

A study in 12 healthy subjects found that nicotinamide riboside at three single doses (100 mg, 300 mg, and 1,000 mg) safely increased blood NAD^+. Two of the participants self-reported skin flushing after taking the 300-mg dose, and two others reported feeling hot following intake of 1,000 mg of nicotinamide riboside (1). In a recent randomized, placebo-controlled trial in 120 healthy adults (ages, 60-80 years), daily supplementation with nicotinamide riboside (250 mg or 500 mg) and pterostilbene (a SIRT activator; 50 mg or 100 mg) for eight weeks showed a favorable side effect profile, with no evidence of higher incidence of adverse effects compared to placebo (129). Most recently, a randomized, placebo-controlled trial in 40 obese men (ages, 40-70 years) found that daily supplementation with nicotinamide riboside (2,000 mg/day divided into two daily dosages) for 12 weeks was associated with reports of only minor side effects, including excessive sweating, pruritus, and mild gastrointestinal symptoms like bloating (139).

The tolerable upper intake level (UL)

Flushing of the skin primarily on the face, arms, and chest is a common side effect of nicotinic acid and may occur initially at doses as low as 30 mg/day. Although flushing from nicotinamide is rare, the Food and Nutrition Board set the tolerable upper intake level (UL) for niacin (nicotinic acid and nicotinamide) at 35 mg/day in adults to avoid the adverse effect of flushing (41). Analysis of data from the US National Health and Nutrition Examination Survey (NHANES) 2003-2006 found that 15.8% of children and adolescents (ages 2-18 years) and 8.5% of adults (≥19 years) had total usual niacin intakes exceeding the UL (130). The UL applies to the general population and is not meant to apply to individuals who are being treated with a nutrient under medical supervision (e.g., high-dose nicotinic acid for elevated blood cholesterol concentrations).

Table 3. Tolerable Upper Intake Level (UL) for Niacin

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	10
Children 4-8 years	15
Children 9-13 years	20
Adolescents 14-18 years	30
Adults 19 years and older	35
*Source of intake should be from food and formula only.	

Drug interactions

The occurrence of rhabdomyolysis is increased in patients treated with statins (HMG-CoA reductase inhibitors). Rhabdomyolysis is a relatively uncommon condition in which muscle cells are broken down, releasing enzymes and electrolytes into the blood, and sometimes resulting in kidney failure (131). Co-administration of nicotinic acid with a statin seems to enhance the risk of rhabdomyolysis (132). A new drug, laropiprant, blocks prostanoid receptors and reduces nicotinic acid-induced flushing (133). A randomized, placebo-controlled trial was designed to identify possible adverse effects of the niacin/laropiprant combination in over 25,000 simvastatin-treated subjects (134). When added to the statin therapy, niacin/laropiprant increased the risk of myopathy and rhabdomyolysis, particularly in Asian subjects. It is possible that the niacin/laropiprant combination further reduces the poor tolerability to statin treatment observed in certain populations (135).

In the three-year, randomized controlled HATS study, concurrent therapy with antioxidants (1,000 mg/day of vitamin C, 800 IU/day of *RRR*-α-tocopherol, 100 μg/day of selenium, and 25 mg/day of β-carotene) diminished the protective effects of the simvastatin-nicotinic acid combination (136). Although the mechanism for these effects is not known, the benefit of concurrent antioxidant therapy in patients on lipid-lowering agents has been questioned (137).

Adverse effects of large doses of nicotinic acid may be exacerbated by the concomitant use of certain medications. The risk of myopathy may be further increased in those taking nicotinic acid and bile acid sequestrants (e.g., cholestyramine, colestipol) or the anti-lipidemic drug, gemfibrozil (Lopid), and the risk of hepatotoxicity observed with nicotinic acid might be enhanced by drugs like paracetamol, amiodarone (Cordarone), or carbamazepine (Tegretol) (35). In addition, large doses of nicotinic acid may reduce uric acid excretion, thereby opposing the action of uricosuric agents like probenecid (Probalan) (35).

Several other medications may interact with niacin therapy or with absorption and metabolism of the vitamin (126). Estrogen and estrogen-containing oral contraceptives increase the efficiency of niacin synthesis from tryptophan, resulting in a decreased dietary requirement for niacin (138). Long-term administration of chemotherapy agents has been reported to cause symptoms of pellagra; therefore, niacin supplementation may be needed (see Pellagra causes).

Linus Pauling Institute Recommendation

The optimum intake of niacin for health promotion and chronic disease prevention is not yet known. The RDA (16 mg NE/day for men and 14 mg NE/day for women) is easily obtainable by consuming a varied diet and should prevent deficiency in most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement, containing 100% of the Daily Value (DV) for niacin, will provide at least 20 mg of niacin daily.

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Pantothenic Acid

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Summary

- Pantothenic acid — also known as vitamin B_5 — is a water-soluble vitamin that is a precursor in the synthesis of coenzyme A. Coenzyme A is essential to many biochemical reactions that sustain life. Also, the phosphopantetheinyl moiety of coenzyme A is required for the biological activity of several proteins, including the acyl-carrier protein involved in fatty acid synthesis. *(More information)*
- Pantothenic acid is essential to all forms of life. It is ubiquitously found in foods of plant and animal origin, and dietary deficiency is very rare. *(More information)*
- The Food and Nutrition Board of the US Institute of Medicine set an adequate intake (AI) of 5 milligrams (mg)/day for adults based on the estimated daily average intake of pantothenic acid. *(More information)*
- Evidence from limited intervention studies suggests that pantothenic acid and/or pantothenol (alcohol analog) might improve the healing process of skin wounds. Yet, additional larger studies are warranted. *(More information)*
- Treatment with high-dose pantethine — a pantothenic acid derivative — has been shown to lower serum cholesterol and lipid concentrations. Although pantethine therapy appears to be well tolerated, medical supervision is indispensable. *(More information)*
- Foods rich in pantothenic acid include animal organs (liver and kidney), fish, shellfish, milk products, eggs, avocados, legumes, mushrooms, and sweet potatoes. *(More information)*
- Little or no toxicity has been associated with dietary and supplemental pantothenic acid such that no tolerable upper intake level (UL) has been set. *(More information)*

Pantothenic acid, also known as vitamin B_5, is essential to all forms of life (1). Pantothenic acid is found throughout all branches of life in the form of coenzyme A, a vital coenzyme in numerous chemical reactions (2).

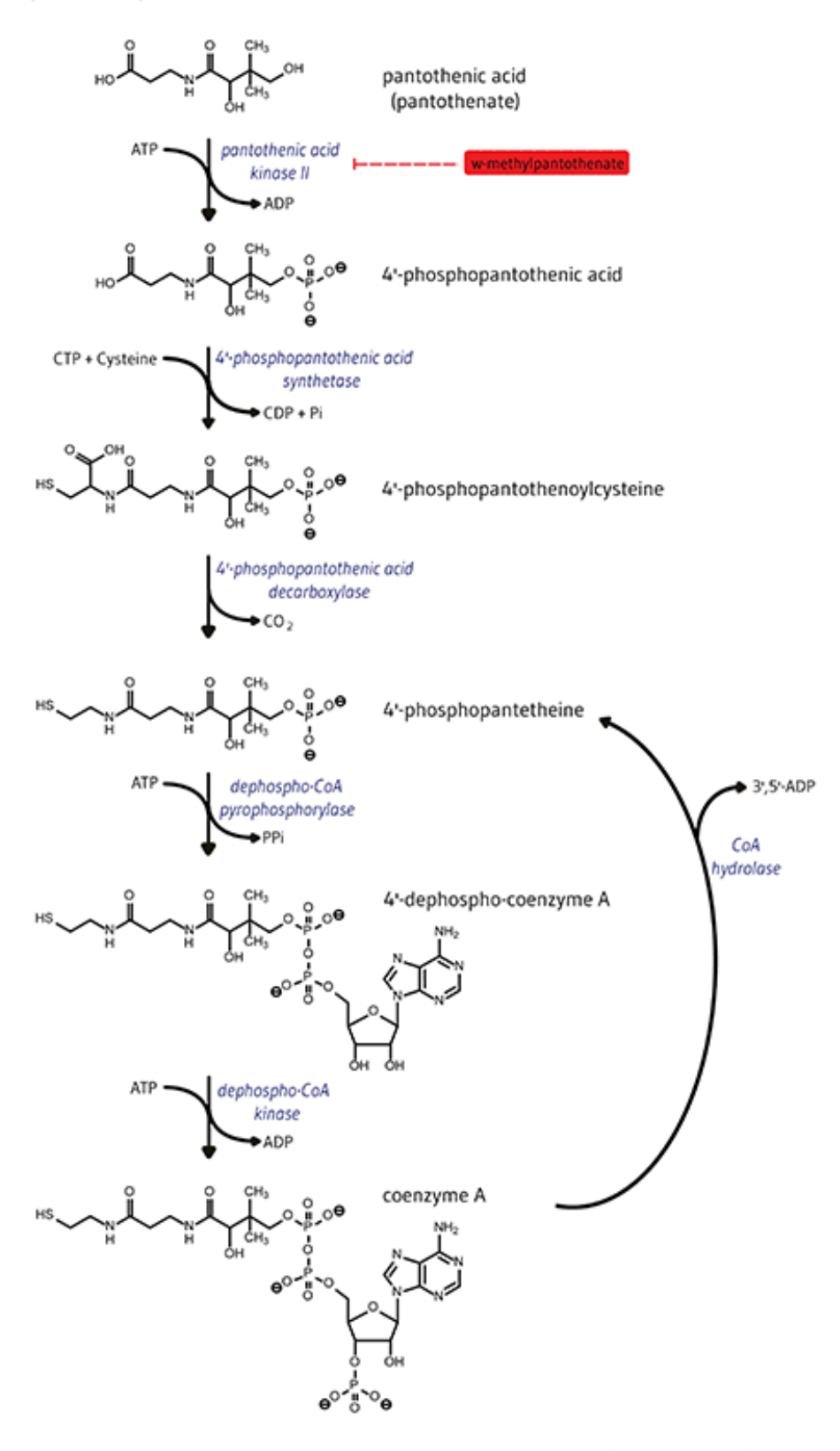
Function

Synthesis of pantothenic acid cofactors

Coenzyme A

Pantothenic acid is a precursor in the biosynthesis of coenzyme A (CoA) (**Figure 1**), an essential coenzyme in a variety of biochemical reactions that sustain life (see below). Pantothenic acid kinase II (PANKII) catalyzes the initial step of phosphorylation of pantothenic acid to 4'-phosphopantothenic acid. Coenzyme A and its derivatives inhibit the synthesis of 4'-phosphopantothenic acid, but the inhibition can be reversed by carnitine, required for the transport of fatty acids into the mitochondria (3). The subsequent reactions in this biosynthetic pathway include the synthesis of the intermediate 4'-phosphopantetheine, as well as the recycling of coenzyme A to 4'-phosphopantetheine (**Figure 1**).

Figure 1. Coenzyme A Synthesis from Pantothenic Acid


pantothenic acid (pantothenate)
ATP
pantothenic acid kinase II
ADP
ω-methylpantothenate
4'-phosphopantothenic acid
CTP + Cysteine
4'-phosphopantothenic acid synthetase
CDP + Pi
4'-phosphopantothenoylcysteine
4'-phosphopantothenic acid decarboxylase
CO_2
4'-phosphopantetheine
ATP
dephospho-CoA pyrophosphorylase
PPi
4'-dephospho-coenzyme A
ATP
dephospho-CoA kinase
ADP
coenzyme A
3',5'-ADP
CoA hydrolase

Pantothenic acid is a precursor in the synthesis of coenzyme A. The initial phosphorylation reaction that converts pantothenic acid into 4'-phosphopantothenic acid is impaired in individuals with an inherited defect in the gene (*PANKII*) coding for pantothenic acid kinase II.

4'-phosphopantetheine

The 4'-phosphopantetheinyl moiety of coenzyme A can be transferred to enzymes in which 4'-phosphopantetheine is an essential cofactor for their biological activities (see 4'-phosphopantetheinylation).

Cofactor and co-substrate function

Coenzyme A

Coenzyme A reacts with acyl groups, giving rise to thioester derivatives, such as acetyl-CoA, succinyl-CoA, malonyl-CoA, and 3-hydroxy-3-methylglutaryl (HMG)-CoA. Coenzyme A and its acyl derivatives are required for reactions that generate energy from the degradation of dietary fat, carbohydrates, and proteins. In addition, coenzyme A in the form of acetyl-CoA and succinyl-CoA is involved in the citric acid cycle, in the synthesis of essential fats, cholesterol, steroid hormones, vitamins A and D, the neurotransmitter acetylcholine, and in the fatty acid β-oxidation pathway. Coenzyme A derivatives are also required for the synthesis of the hormone, melatonin, and for a component of hemoglobin called heme. Further, metabolism of a number of drugs and toxins by the liver requires coenzyme A (4).

Coenzyme A was named for its role in acetylation reactions. Most acetylated proteins in the body have been modified by the addition of an acetate group that was donated by the coenzyme A thioester derivative, acetyl-CoA. Protein acetylation alters the overall charge of proteins, modifying their three-dimensional structure and, potentially, their function. For example, acetylation is a mechanism that regulates the activity of peptide hormones, including those produced by the pituitary gland (5). Also, protein acetylation, like other posttranslational modifications, has been shown to regulate the subcellular localization, the function, and the half-life of many signaling molecules, transcription factors, and enzymes. Notably, the acetylation of histones plays a role in the regulation of gene expression by facilitating transcription (i.e., mRNA synthesis), while deacetylated histones are usually associated with chromatin compaction and gene silencing. The acetylation of histones was found to result in structural changes of the chromatin, which affect both DNA-protein and protein-protein interactions. Crosstalk between acetylation marks and other posttranscriptional modifications of the histones also facilitate the recruitment of transcriptional regulators to the promoter of genes that are subsequently transcribed (reviewed in 6).

Finally, a number of signaling molecules are modified by the attachment of long-chain fatty acids donated by coenzyme A. These modifications are known as protein acylation and have central roles in cell-signaling pathways (4).

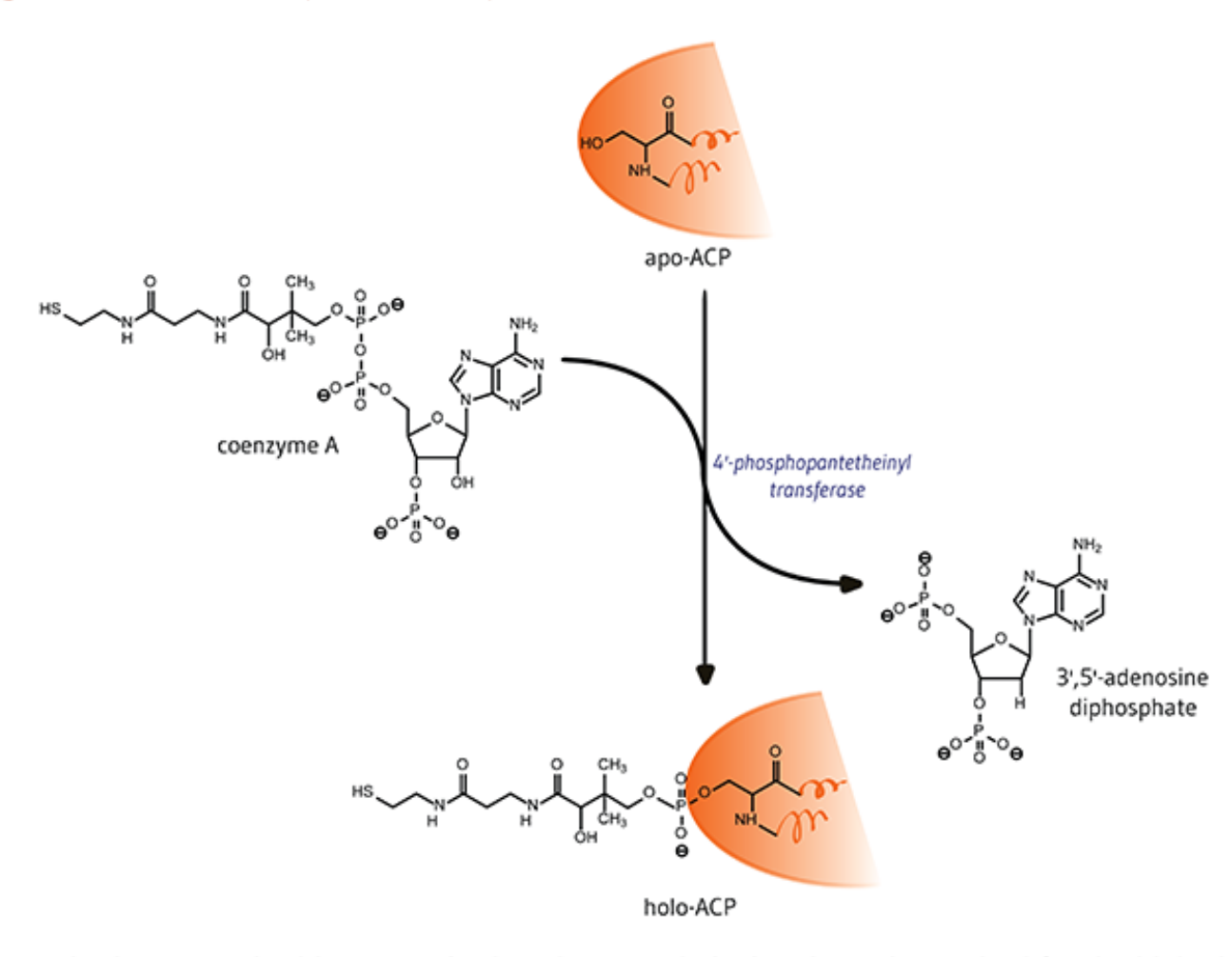
4'-phosphopantetheinylation

Specific multi-enzyme complexes, which need to carry out several reactions in an orderly manner, may require the covalent attachment of a 4'-phosphopantetheine arm to a "carrier" domain (or protein). This carrier domain holds substrates or reaction intermediates during the progression through the various enzymatic reactions. In mammals, the transfer of the 4'-phosphopantetheinyl moiety from coenzyme A to a conserved serine residue of a specific carrier domain is catalyzed by one unique phosphopantetheinyl transferase (7). The 4'-phosphopantetheinylation is necessary for the conversion of apo-enzymes into fully active holo-enzymes (see below).

Acyl-carrier protein

Lipids are fat molecules essential for normal physiological function and, among other types, include sphingolipids (essential components of the myelin sheath that enhances nerve transmission), phospholipids (important structural components of cell membranes), and fatty acids. Fatty acid synthase (FAS) is a multi-enzyme complex that catalyzes the synthesis of fatty acids. Within the FAS complex, the acyl-carrier protein (ACP) requires pantothenic acid in the form of 4'-phosphopantetheine for its activity as a carrier protein (3). A group, such as the 4'-phosphopantetheinyl moiety for ACP, is called a prosthetic group; the prosthetic group is not composed of amino acids and is a tightly bound cofactor required for the biological activity of some proteins (**Figure 2**). Acetyl-CoA, malonyl-CoA, and ACP are all required for the synthesis of fatty acids in the cytosol. During fatty acid synthesis, the acyl groups of acetyl-CoA and malonyl-CoA are transferred to the sulfhydryl group (-SH) of the 4'-phosphopantetheinyl moiety of ACP. The prosthetic group is used as a flexible arm to transfer the growing fatty acid chain to each of the enzymatic centers of the type I FAS complex. In the mitochondria, 4'-phosphopantetheine also serves as a prosthetic group for an ACP homolog present in mitochondrial type II FAS complex (8).

Figure 2. 4'-Pantetheinylation of Acyl-Carrier Protein (ACP)

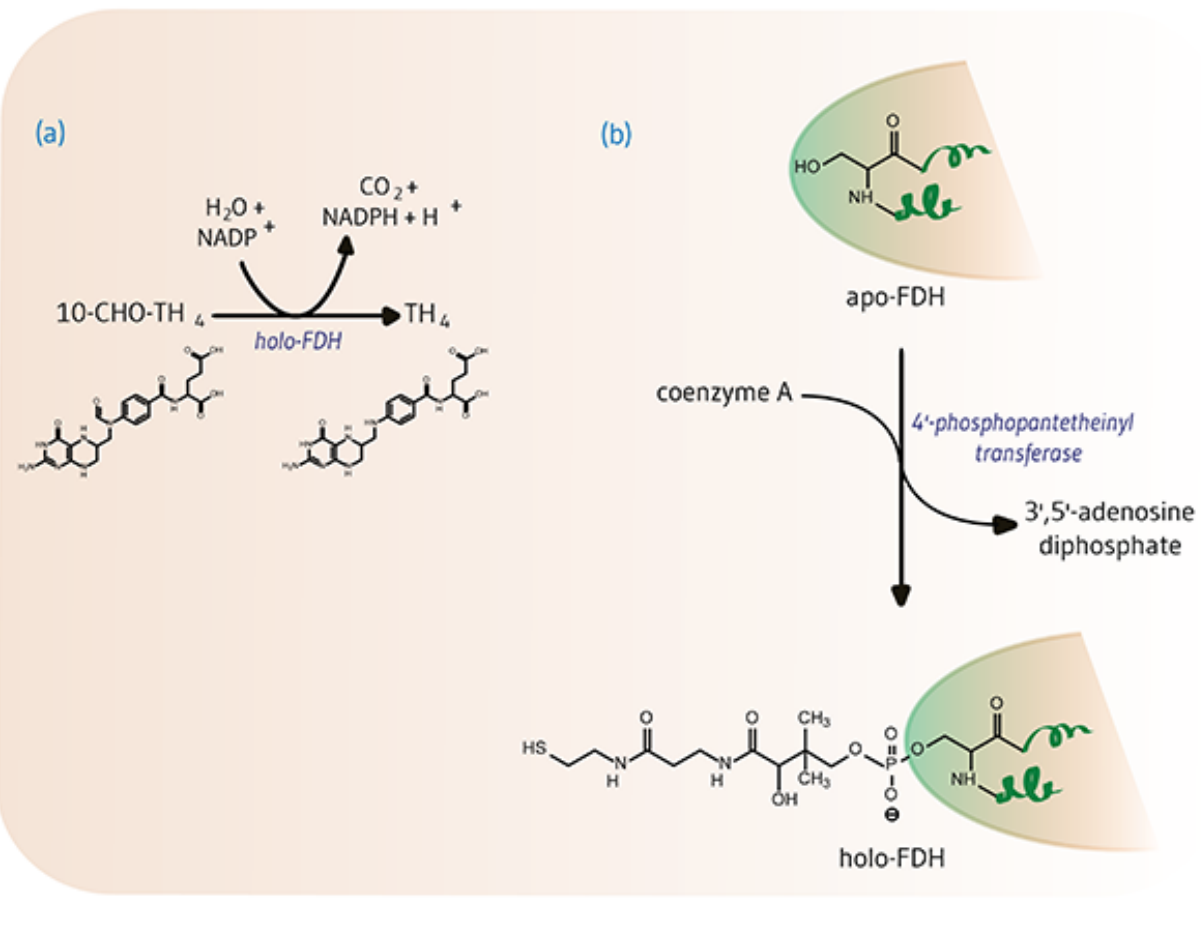

apo-ACP
coenzyme A
4'-phosphopantetheinyl transferase
3',5'-adenosine diphosphate
holo-ACP

A prosthetic group – in this case, a 4'-phosphopantetheinyl moiety – is required for the biological function of ACP. The addition of the prosthetic group occurs after ACP synthesis (post-translation) in a reaction catalyzed by 4'-phosphopantetheinyl transferase. The enzyme catalyzes the hydrolysis of coenzyme A to 3',5'-adenosine diphosphate and 4'-phosphopantetheine, and the transfer of the 4'-phosphopantetheinyl moiety to a serine residue at the active site of ACP. *ACP, acyl-carrier protein; apo-ACP, biologically inactive ACP; holo-ACP, biologically active ACP.*

10-formyltetrahydrofolate dehydrogenase

The enzyme 10-formyltetrahydrofolate dehydrogenase (FDH) catalyzes the conversion of 10-formyltetrahydrofolate to tetrahydrofolate, an essential cofactor in the metabolism of nucleic acids and amino acids (**Figure 3**). Similar to ACP, FDH requires a 4'-phosphopantetheine prosthetic group for its biological activity. The prosthetic group acts as a swinging arm to couple the activities of the two catalytic domains of FDH (9, 10). A homolog of FDH in mitochondria also requires 4'-phosphopantetheinylation to be biologically active (11).

Figure 3. 4'-Pantetheinylation of Formyltetrahydrofolate Dehydrogenase (FDH)

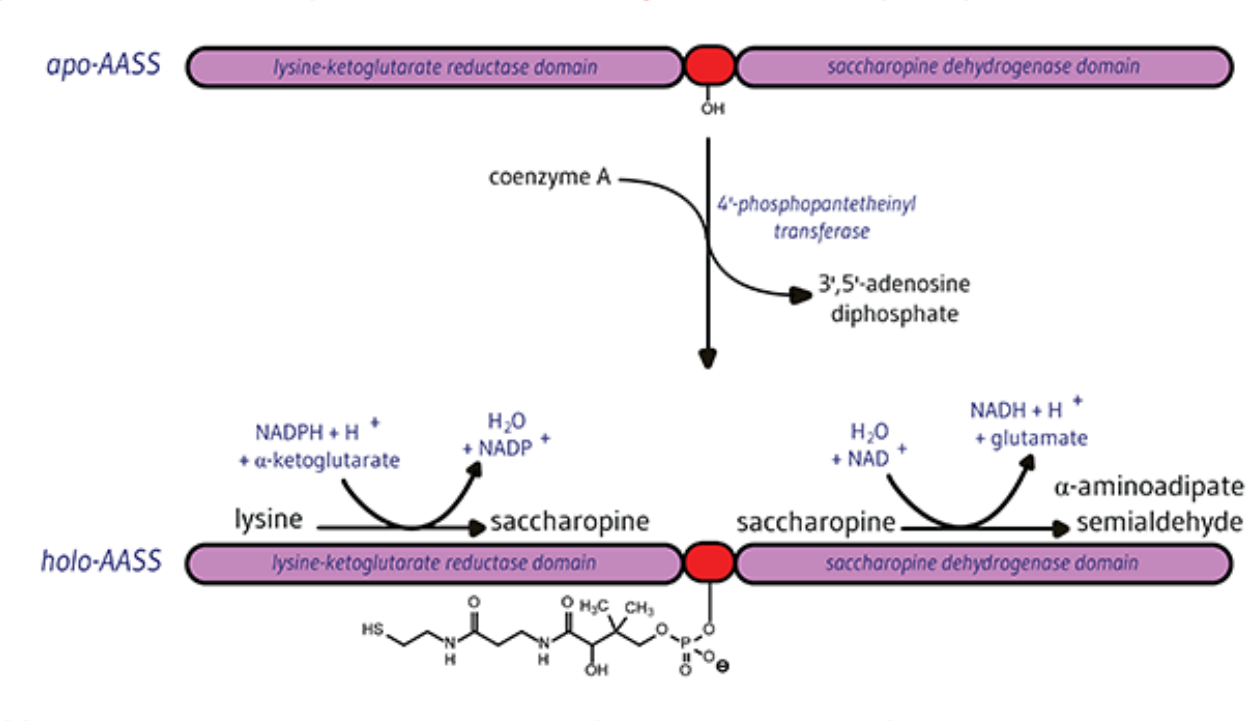


(a) The generation of TH_4 from 10-CHO-TH_4 is catalyzed by FDH, an enzyme requiring 4'-phosphopantetheine as a prosthetic group to be biologically active. Of note, 10-CHO-TH_4 can also be hydrolyzed to TH_4 (and formate) in another reaction catalyzed by formyltetrahydrofolate deformylase. (b) The enzyme 4'-phosphopantetheinyl transferase catalyzes the transfer of a 4'-phosphopantetheinyl moiety from coenzyme A to a specific serine residue of FDH, converting apo-FDH to holo-FDH. *FDH, formyltetrahydrofolate dehydrogenase; apo-FDH, biologically inactive FDH; holo-FDH, biologically active FDH; 10-CHO-TH_4, 10-formyltetrahydrofolate; TH_4, tetrahydrofolate; $NADP^+$/NADPH, nicotinamide adenine dinucleotide phosphate oxidized/reduced.*

α-Aminoadipate semialdehyde synthase

4'-phosphopantetheinylation is required for the biological activity of the apo-enzyme α-aminoadipate semialdehyde synthase (AASS). AASS catalyzes the initial reactions in the mitochondrial pathway for the degradation of lysine — an essential amino acid for humans. AASS is made of two catalytic domains. The lysine-ketoglutarate reductase domain first catalyzes the conversion of lysine to saccharopine. Saccharopine is further converted to α-aminoadipate semialdehyde in a reaction catalyzed by the saccharopine dehydrogenase domain (**Figure 4**).

Figure 4. 4'-Pantetheinylation of α-Aminoadipate Semialdehyde Synthase (AASS)


apo-AASS
lysine-ketoglutarate reductase domain
saccharopine dehydrogenase domain
OH
coenzyme A
4'-phosphopantetheinyl transferase
3',5'-adenosine diphosphate
$NADPH + H^+$ + α-ketoglutarate
$H_2O + NADP^+$
lysine
saccharopine
$H_2O + NAD^+$
$NADH + H^+$ + glutamate
α-aminoadipate semialdehyde
holo-AASS

AASS is a mitochondrial enzyme responsible for the conversions of lysine to saccharopine and saccharopine to α-aminoadipate semialdehyde in the mitochondrial pathway for lysine degradation. The first reaction is catalyzed by the lysine-ketoglutarate reductase domain of AASS, and the saccharopine dehydrogenase domain catalyzes the second reaction. Apo-AASS requires 4'-phosphopantetheine as a prosthetic group to be biologically active. The enzyme 4'-phosphopantetheinyl transferase catalyzes the transfer of a 4'-phosphopantetheinyl moiety from coenzyme A to a specific residue of AASS, converting apo-AASS to holo-AASS. The 4'-phosphopantetheinyl arm is thought to serve as a swinging arm that couples the activities of the two enzymatic domains of AASS. *AASS, α-aminoadipate semialdehyde synthase.*

Deficiency

Naturally occurring pantothenic acid deficiency in humans is very rare and has been observed only in cases of severe malnutrition. World War II prisoners in the Philippines, Burma, and Japan experienced numbness and painful burning and tingling in their feet; these symptoms were relieved specifically by pantothenic acid supplementation (4). Pantothenic acid deficiency in humans has been induced experimentally by co-administering a pantothenic acid kinase inhibitor (ω-methylpantothenate; see **Figure 1** above) and a pantothenic acid-deficient diet. Participants in this experiment complained of headache, fatigue, insomnia, intestinal disturbances, and numbness and tingling of their hands and feet (12). In another study, participants fed only a pantothenic acid-free diet did not develop clinical signs of deficiency, although some appeared listless and complained of fatigue (13).

Calcium homopantothenate (or hopantenate) is a pantothenic acid antagonist with cholinergic effects (i.e., similar to those of the neurotransmitter, acetylcholine). This compound is used in Japan to enhance mental function, especially in Alzheimer's disease. A rare side effect was the development of hepatic encephalopathy, a condition of abnormal brain function resulting from the failure of the liver to eliminate toxins. The encephalopathy was reversed by pantothenic acid supplementation, suggesting that it was due to homopantothenate-induced pantothenic acid deficiency (14). Of note, genetic mutations in the human gene *PANKII*, which codes for pantothenic acid kinase II (see **Figure 1** above), result in impaired synthesis of 4'-phosphopantetheine and coenzyme A (see Function). The disorder, called pantothenate kinase-associated neurodegeneration, is characterized by visual and intellectual impairments, dystonia, speech abnormalities, behavioral difficulties, and personality disorders (15).

Yet, because pantothenic acid is widely distributed in nature and deficiency is extremely rare in humans, most information regarding the consequences of deficiency has been gathered from experimental research in animals (reviewed in 3). Pantothenic acid-deficient rats developed damage to the adrenal glands, while monkeys developed anemia due to decreased synthesis of heme, a component of hemoglobin. Dogs with pantothenic acid deficiency developed low blood glucose, rapid breathing and heart rates, and convulsions. Chickens developed skin irritation, feather abnormalities, and spinal nerve damage associated with the degeneration of the myelin sheath. Pantothenic acid-deficient mice showed decreased exercise tolerance and diminished storage of glucose (in the form of glycogen) in muscle and liver. Mice also developed skin irritation and graying of the fur, which is reversed by pantothenic acid administration.

The diversity of symptoms emphasizes the numerous functions of pantothenic acid in its coenzyme forms.

The Adequate Intake (AI)

Because there was little information on the requirements of pantothenic acid in humans, the Food and Nutrition Board of the Institute of Medicine set an adequate intake (AI) based on observed dietary intakes in healthy population groups (**Table 1**) (16).

Table 1. Adequate Intake (AI) for Pantothenic Acid

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	1.7	1.7
Infants	7-12 months	1.8	1.8
Children	1-3 years	2	2
Children	4-8 years	3	3
Children	9-13 years	4	4
Adolescents	14-18 years	5	5
Adults	19 years and older	5	5
Pregnancy	all ages	-	6
Breast-feeding	all ages	-	7

Disease Treatment

Wound healing

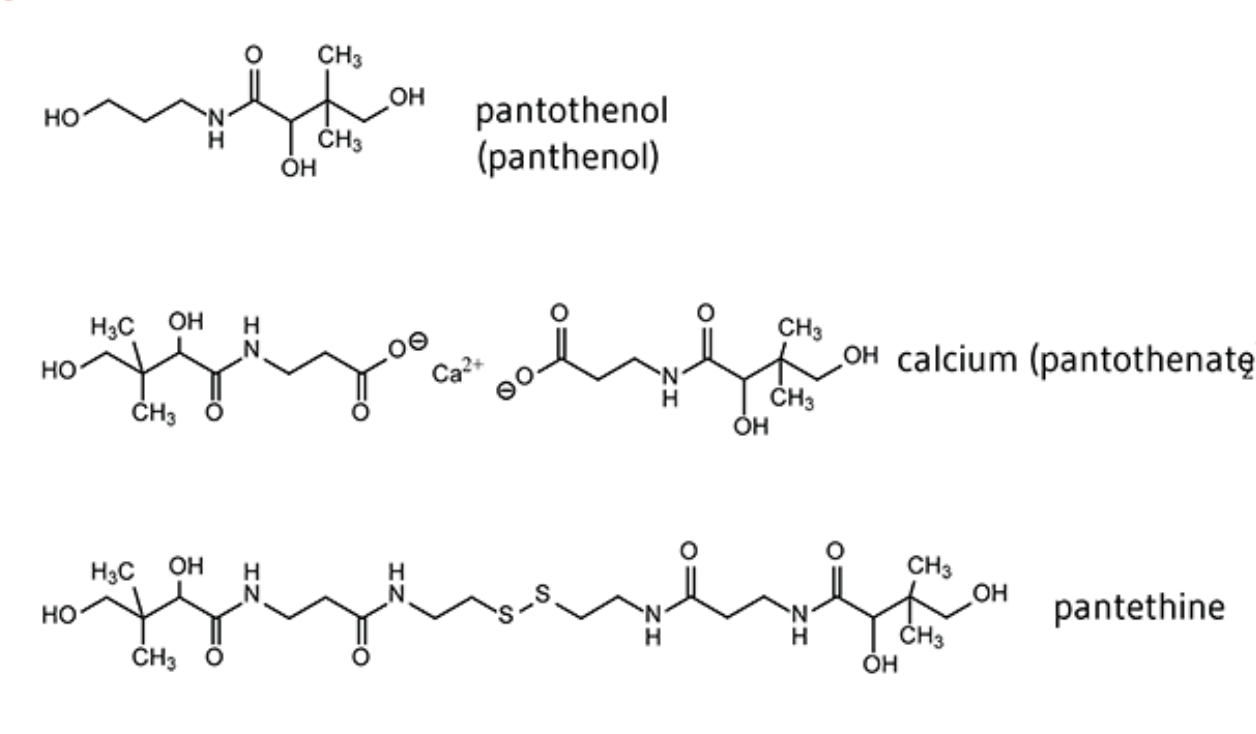
The addition of calcium D-pantothenate and/or pantothenol (**Figure 5**) to the medium of cultured skin fibroblasts given an artificial wound was found to increase cell proliferation and migration, thus accelerating wound healing *in vitro* (17, 18). Likewise, *in vitro* deficiency in pantothenic acid induced the expression of differentiation markers in proliferating skin fibroblasts and inhibited proliferation in human keratinocytes (19). The application of ointments containing either calcium D-pantothenate or pantothenol — also known as D-panthenol or dexpanthenol — to the skin has been shown to accelerate the closure of skin wounds and increase the strength of scar tissue in animals (3).

The effects of dexpanthenol on wound healing are unclear. In a placebo-controlled study that included 12 healthy volunteers, the application of dexpanthenol-containing ointment (every 12 hours for 1 to 6 days) in a model of skin wound healing was associated with an enhanced expression of markers of proliferation, inflammation, and tissue repair (20). However, the study failed to report whether these changes in response to topical dexpanthenol improved the wound-repair process compared to placebo (20). Some studies have shown no effects. Early randomized controlled trials in patients undergoing surgery for tattoo removal found that daily co-supplementation with 1 gram or 3 grams of vitamin C and 200 mg or 900 mg of pantothenic acid for 21 days did not significantly improve the wound-healing process (21, 22). Yet, in a recent randomized, double-blind, placebo-controlled study, the use of dexpanthenol pastilles (300 mg/day for up to 14 days post surgery) was found to accelerate mucosal healing after tonsillectomy in children (23).

High cholesterol

Early studies suggested that pharmacologic doses of pantethine, a pantothenic acid derivative, might have a cholesterol-lowering effect (24, 25). Pantethine is made of two molecules of pantetheine joined by a disulfide bond (chemical bond between two molecules of sulfur) (**Figure 5**). Pantethine is structurally related to coenzyme A and is found in the prosthetic group that is required for the biological function of acyl-carrier protein, formyltetrahydrofolate dehydrogenase, and α-aminoadipate semialdehyde synthase (see Function). In a 16-week, randomized, double-blind, placebo-controlled study, daily pantethine supplementation (600 mg/day for 8 weeks, followed by 900 mg/day for another 8 weeks) significantly improved the profile of lipid parameters in 120 individuals at low-to-moderate risk of cardiovascular disease (CVD). After adjusting to baseline, pantethine was found to be significantly more effective than placebo in lowering the concentrations of low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB), as well as reducing the ratio of triglycerides to high-density lipoprotein-cholesterol (TG:HDL-C) (26). Although it appears to be well tolerated and potentially beneficial in improving cholesterol metabolism, pantethine is not a vitamin, and the decision to use pharmacologic doses of pantethine to treat elevated blood cholesterol or triglycerides should only be made in collaboration with a qualified health care provider who provides appropriate follow up.

Figure 5. Chemical Structures of Some Pantothenic Acid Derivatives



Graying of hair

Mice that are deficient in pantothenic acid developed skin irritation and graying of the fur, which is reversed by pantothenic acid administration. In humans, there is no evidence that taking pantothenic acid as supplements or using shampoos containing pantothenic acid can prevent or restore hair color.

Sources

Food sources

Pantothenic acid is available in a variety of foods, usually as a component of coenzyme A (CoA) and 4'-phosphopantetheine (see **Figure 1** above). Upon ingestion, dietary coenzyme A and phosphopantetheine are hydrolyzed to pantothenic acid prior to intestinal absorption (3). Animal liver and kidney, fish, shellfish, pork, chicken, egg yolk, milk, yogurt, legumes, mushrooms, avocados, broccoli, and sweet potatoes are good sources of pantothenic acid. Whole grains are also good sources of pantothenic acid, but processing and refining grains may result in a 35 to 75% loss. Freezing and canning of foods result in similar losses (16). Large national, nutritional surveys failed to estimate pantothenic acid intake, mainly because of the scarcity of data on the pantothenic acid content of food (16). Smaller studies estimated average daily intakes of pantothenic acid to be between 4 and 7 mg/day in adults. **Table 2** lists some rich sources of pantothenic acid, along with their content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Pantothenic Acid

Food	Serving	Pantothenic Acid (mg)
Beef liver (cooked, pan fried)	3 ounces*	5.6
Sunflower seed kernels (dry roasted)	1 ounce	2.0
Fish, trout (mixed species, cooked, dry heat)	3 ounces*	1.9
Yogurt (plain, nonfat)	8 ounces	1.6
Lobster (cooked)	3 ounces	1.4
Avocado (raw, California)	½ fruit	1.0
Sweet potato (cooked, with skin)	1 medium (½ cup)	1.0
Milk	1 cup (8 fluid ounces)	0.87
Pork (tenderloin, lean, cooked, roasted)	3 ounces*	0.86
Chicken (light meat, cooked, roasted)	3 ounces*	0.83
Egg (cooked, hard-boiled)	1 large	0.70
Cheese, feta	½ cup (crumbled)	0.70
Lentils (mature seeds, cooked, boiled)	½ cup	0.63
Split peas (mature seeds, cooked, boiled)	½ cup	0.58
Mushrooms (white, raw)	½ cup (chopped)	0.52
Peanuts	1 ounce	0.50
Broccoli (cooked, boiled)	½ cup (chopped)	0.48
Orange	1 whole	0.30
Whole-wheat bread	1 slice	0.21
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Intestinal bacteria

The bacteria that normally colonize the colon (large intestine) are capable of synthesizing pantothenic acid. A specialized transporter for the uptake of biotin and pantothenic acid was identified in cultured cells derived from the lining of the colon, suggesting that humans may be able to absorb pantothenic acid and biotin produced by intestinal bacteria (27). However, the extent to which bacterial synthesis contributes to pantothenic acid intake in humans is not known (28).

Supplements

Pantothenol and pantothenate

Supplements commonly contain pantothenol (panthenol), a stable alcohol analog of pantothenic acid, which can be rapidly converted to pantothenic acid by humans. Calcium and sodium D-pantothenate, the calcium and sodium salts of pantothenic acid, are also available as supplements.

Pantethine

Pantethine is used as a cholesterol-lowering agent in Japan and is available in the US as a dietary supplement (29).

Safety

Toxicity

Pantothenic acid is not known to be toxic in humans. The only adverse effect noted was diarrhea resulting from very high intakes of 10 to 20 g/day of calcium D-pantothenate (30). However, there is one case report of life-threatening eosinophilic pleuropericardial effusion in an elderly woman who took a combination of 10 mg/day of biotin and 300 mg/day of pantothenic acid for two months (31). Due to the lack of reports of adverse effects when the Dietary Reference Intakes (DRI) for pantothenic acid were established in 1998, the Food and Nutrition Board of the Institute of Medicine did not establish a tolerable upper intake level (UL) for pantothenic acid (16). Pantethine is generally well tolerated in doses up to 1,200 mg/day. However, gastrointestinal side effects, such as nausea and heartburn, have been reported (29). Also, topical formulations containing up to 5% of dexpanthenol (D-panthenol) have been safely used for up to one month. Yet, a few cases of skin irritation, contact dermatitis, and eczema have been reported with the use of dexpanthenol-containing ointments (32, 33).

Nutrient interactions

Large doses of pantothenic acid have the potential to compete with biotin for intestinal and cellular uptake by the human sodium-dependent multivitamin transporter (hSMVT) (27, 34).

Drug interactions

Oral contraceptives (birth control pills) containing estrogen and progestin may increase the requirement for pantothenic acid (30). Use of pantethine in combination with cholesterol-lowering drugs called statins (HMG-CoA reductase inhibitors) or with nicotinic acid (see the article on Niacin) may produce additive effects on blood lipids (29).

Linus Pauling Institute Recommendation

More data are needed to define the amount of dietary pantothenic acid required to promote optimal health or prevent chronic disease. The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 5 mg/day of pantothenic acid for adults. A varied diet should provide enough pantothenic acid for most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement that contains 100% of the Daily Value (DV) for pantothenic acid will ensure an intake of at least 5 mg/day.

Older adults (>50 years)

There is currently little evidence that older adults differ in their intake of or their requirement for pantothenic acid. Most multivitamin/mineral supplements provide at least 5 mg/day of pantothenic acid.

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Riboflavin

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Summary

- Riboflavin is the precursor of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). FAD and FMN act as electron carriers in a number of oxidation-reduction (redox) reactions involved in energy production, cellular antioxidant function, and in numerous metabolic pathways. *(More information)*
- Riboflavin (as FAD or FMN) is required for the metabolism of iron and vitamin B_6, and in the synthesis of niacin from tryptophan. It also plays an essential role in folate and related one-carbon metabolism, where FAD is required as a cofactor for methylenetetrahydrofolate reductase (MTHFR), a key folate-metabolizing enzyme. *(More information)*
- Clinical signs of riboflavin deficiency include skin disorders, angular stomatitis, cheilosis, glossitis, and corneal vascularization. Riboflavin deficiency occurs commonly in low- and middle-income countries. *(More information)*
- Subclinical deficiency (low status) of riboflavin without clinical signs may be widespread, including in high-income countries, but it usually goes undetected because riboflavin biomarkers are very rarely measured in human studies. *(More information)*
- Low riboflavin status is associated with preeclampsia in pregnant women, a condition that may progress to eclampsia and cause severe bleeding and death *(More information)*. It is also linked with cataracts in older individuals. *(More information)*
- Deficient/low status of riboflavin interferes with the metabolism of folate, particularly in individuals with the variant 677TT genotype in *MTHFR*. There is some evidence that these individuals exhibit a higher risk of cancer. *(More information)*
- Case reports have shown that patients with autosomal recessive disorders of riboflavin metabolism may benefit from riboflavin supplementation. *(More information)*
- The *MTHFR* C677T polymorphism is associated with an increased risk of hypertension. Intervention studies have shown that supplementation with riboflavin (the MTHFR cofactor) effectively lowers blood pressure, specifically in individuals with the variant *MTHFR* 677TT genotype. *(More information)*
- Riboflavin supplementation has been evaluated as a prophylactic agent for migraine headache, but the results are conflicting. *(More information)*
- Riboflavin supplementation has been studied as a potential adjunct therapy in cancer, certain eye disorders, and multiple sclerosis. *(More information)*

Riboflavin is a water-soluble B vitamin, also known as vitamin B_2. Riboflavin is primarily found as an integral component of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) (1). Coenzymes derived from riboflavin are termed flavocoenzymes, and enzymes that use a flavocoenzyme are called flavoproteins (2).

Function

Oxidation-reduction (redox) reactions

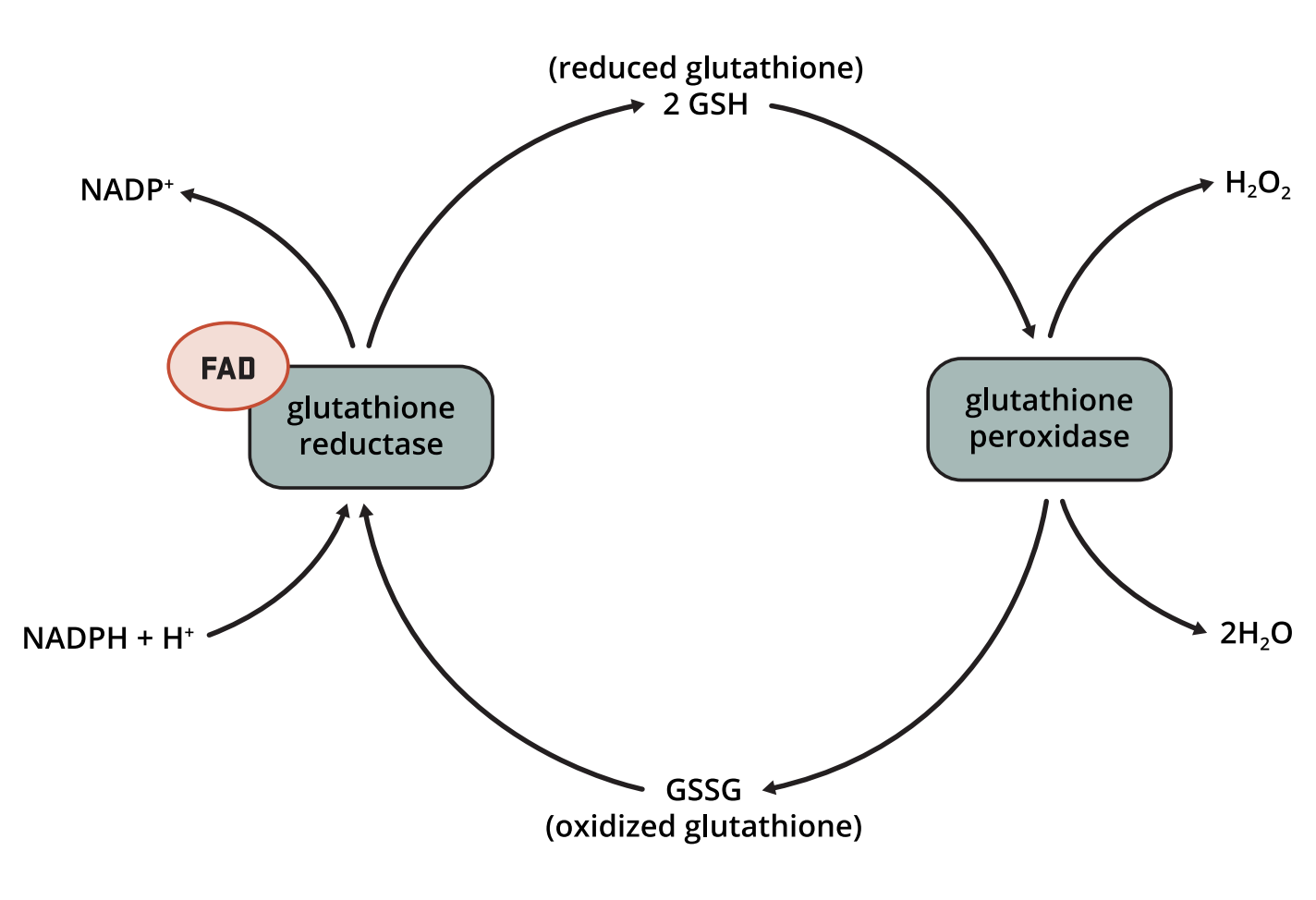
Living organisms derive most of their energy from redox reactions, which are processes that involve the transfer of electrons. Flavocoenzymes participate in redox reactions in numerous metabolic pathways (3). They are critical for the metabolism of carbohydrates, lipids, and proteins. FAD is part of the electron transport (respiratory) chain, which is central to energy production. In conjunction with cytochrome P-450, flavocoenzymes also participate in the metabolism of drugs and toxins (4).

Antioxidant functions

Glutathione reductase is a FAD-dependent enzyme that participates in the redox cycle of glutathione. The glutathione redox cycle plays a major role in protecting organisms from reactive oxygen species, such as hydroperoxides. Glutathione reductase requires FAD to regenerate two molecules of reduced glutathione from oxidized glutathione. Riboflavin deficiency has been associated with increased oxidative stress (4) Measurement of glutathione reductase activity in red blood cells is commonly used to assess riboflavin nutritional status (5).

Glutathione peroxidases (GPx), selenium-containing enzymes, require two molecules of reduced glutathione to break down hydroperoxides. GPx are involved in the glutathione oxidation-reduction (redox) cycle (**Figure 1**).

Figure 1. Glutathione Oxidation-Reduction (Redox) Cycle



FAD - flavin adenine dinucleotide (one of the two cofactor forms of riboflavin)

One molecule of hydrogen peroxide is reduced to two molecules of water, while two molecules of glutathione (GSH) are oxidized in a reaction catalyzed by the selenoenzyme, glutathione peroxidase. Oxidized glutathione (GSSG) may be reduced by the flavin adenine dinucleotide (FAD)-dependent enzyme, glutathione reductase.

Xanthine oxidase, another FAD-dependent enzyme, catalyzes the oxidation of hypoxanthine and xanthine to uric acid. Uric acid is one of the most effective water-soluble antioxidants in the blood. Riboflavin deficiency can result in decreased xanthine oxidase activity, reducing blood uric acid levels (6).

Nutrient interactions

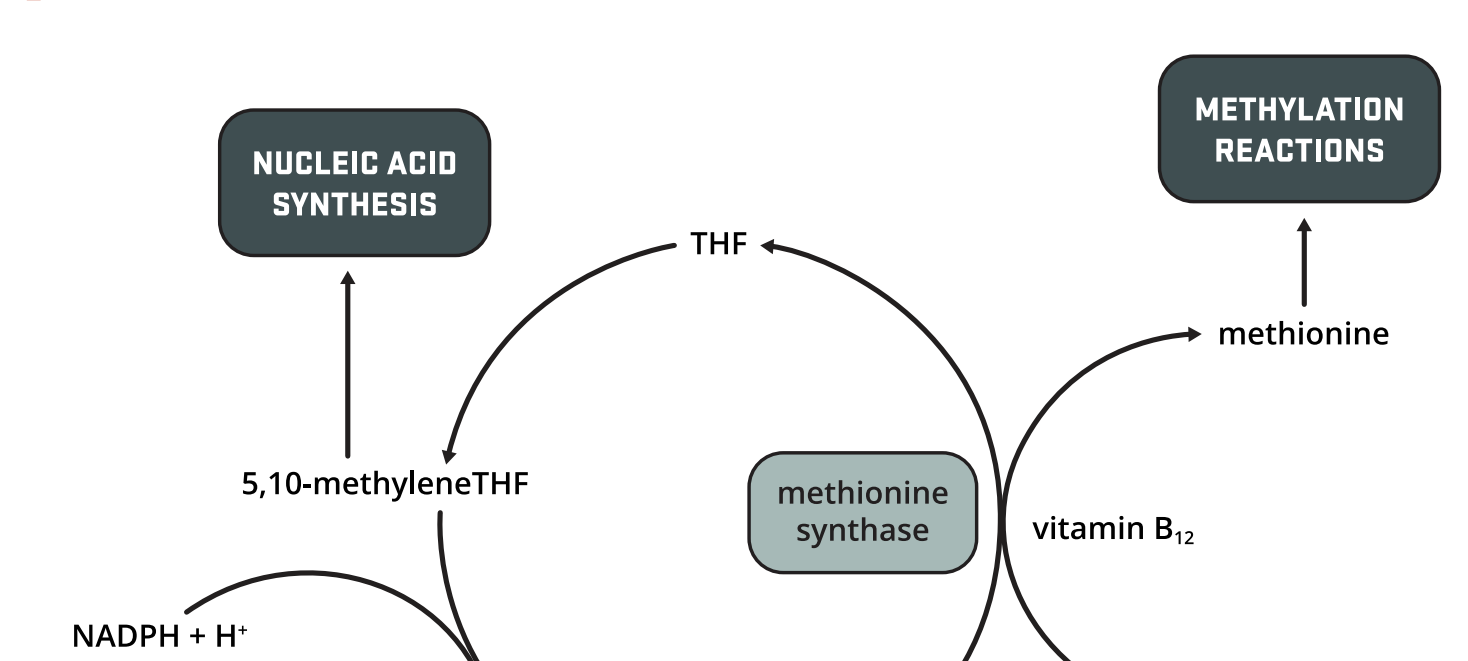
Riboflavin (as FAD or FMN) is required for the synthesis of niacin from tryptophan, and in the metabolism of vitamin B_6 and iron. It is also essential for folate and related one-carbon metabolism, where FAD is required as a cofactor for methylenetetrahydrofolate reductase (MTHFR), a key folate-metabolizing enzyme.

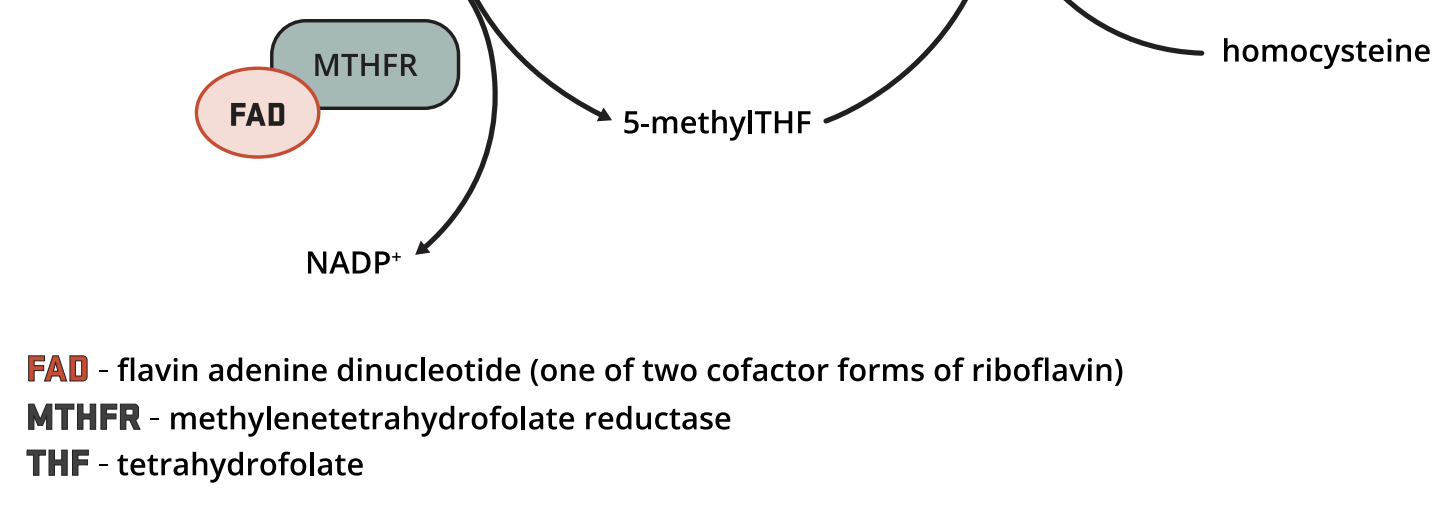
B-complex vitamins

Flavoproteins are involved in the metabolism of several other vitamins: vitamin B_6, niacin, vitamin B_{12}, and folate. Therefore, low and deficient riboflavin status can affect several enzyme systems. The conversion of vitamin B_6 to its active coenzyme form in tissues, pyridoxal 5'-phosphate (PLP), requires the FMN-dependent enzyme, pyridoxine 5'-phosphate oxidase (PPO) (7). Human studies have provided evidence of the metabolic dependency of vitamin B_6 on riboflavin status in older (8-10) and younger (10) adults. The synthesis of the niacin-containing coenzymes, NAD and NADP, from the amino acid tryptophan, requires the FAD-dependent enzyme, kynurenine 3-monooxygenase. Severe riboflavin deficiency can thus decrease the conversion of tryptophan to NAD and NADP, increasing the risk of niacin deficiency (3).

Methylenetetrahydrofolate reductase (MTHFR) is an FAD-dependent enzyme that plays a key role in one-carbon metabolism by catalyzing the reduction of 5,10 methyleneTHF to 5 methylTHF. Once formed, 5 methylTHF is used by methionine synthase for the vitamin B_{12}-dependent conversion of homocysteine to methionine and the formation of THF (**Figure 2**). Both FMN and FAD are coenzymes for the enzyme methionine synthase reductase, which is responsible for the regeneration of methylcobalamin, the biologically active form of vitamin B_{12} acting as a coenzyme for methionine synthase (11). Along with other B vitamins (folate, vitamin B_{12}, and vitamin B_6), higher dietary riboflavin intakes have been associated with lower plasma concentrations of homocysteine (12). In individuals homozygous for the C677T polymorphism in the *MTHFR* gene, low riboflavin status is associated with elevated plasma homocysteine, and in turn linked with a higher risk of cardiovascular disease and other chronic diseases (13, 14). Furthermore, supplementation with riboflavin results in marked lowering of homocysteine concentrations specifically in individuals with the variant *MTHFR* 677TT genotype (15). Such results illustrate that chronic disease risk may be influenced by complex interactions between genetic and dietary factors.

Figure 2. Folate and Nucleic Acid Metabolism





homocysteine
MTHFR
FAD
5-methylTHF
NADP⁺
FAD - flavin adenine dinucleotide (one of two cofactor forms of riboflavin)
MTHFR - methylenetetrahydrofolate reductase
THF - tetrahydrofolate

5,10-methyleneTHF is required for the synthesis of nucleic acids, and 5-methylTHF is required for the formation of methionine from homocysteine. Methionine, in the form of S-adenosylmethionine, is required for many methylation reactions, including DNA methylation. MTHFR is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methyleneTHF to 5-methylTHF.

Iron

Riboflavin deficiency alters iron metabolism. Although the mechanism is not clear, research in animals suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin (16). In humans, low dietary intake of riboflavin has been associated with an increased risk for anemia (17), and improving riboflavin nutritional status has been found to increase circulating hemoglobin levels (18). Correction of riboflavin deficiency in individuals who are both riboflavin and iron deficient improves the response of iron-deficiency anemia to iron therapy (19). Anemia during pregnancy, a worldwide public health problem, is responsible for considerable perinatal morbidity and mortality (20, 21). The management of maternal anemia typically involves supplementation with iron alone or iron in combination with folic acid (22). It is possible that the inclusion of riboflavin could enhance the effects of iron-folic acid supplementation in treating maternal anemia, but the evidence is limited. There are, however, randomized, double-blind intervention trials conducted in pregnant women with anemia in Southeast Asia showing that a combination of folic acid, iron, vitamin A, and riboflavin improved hemoglobin levels and decreased anemia prevalence compared to iron-folic acid supplementation alone (23, 24).

Deficiency

Ariboflavinosis is the medical name for clinical riboflavin deficiency, which occurs commonly in low- and middle-income countries. Riboflavin deficiency is rarely found in isolation; it typically occurs in combination with deficiencies of other water-soluble vitamins. Clinical signs of riboflavin deficiency include sore throat, redness and swelling of the lining of the mouth and throat, cracks or sores on the outsides of the lips (cheliosis) and at the corners of the mouth (angular stomatitis), inflammation and redness of the tongue (magenta tongue), and a moist, scaly skin inflammation (seborrheic dermatitis). Other signs may involve the formation of blood vessels in the clear covering of the eye (vascularization of the cornea) and decreased red blood cell count in which the existing red blood cells contain normal levels of hemoglobin and are of normal size (normochromic normocytic anemia) (1, 3). Subclinical deficiency (low status) of riboflavin without clinical signs may be widespread, including in high-income countries, but usually goes undetected because riboflavin biomarkers are very rarely measured in human studies. Low or deficient riboflavin status may result in decreased conversion of vitamin B$_6$ to its active coenzyme form (PLP) and decreased conversion of tryptophan to niacin (see Nutrient interactions).

Preeclampsia is defined as the presence of elevated blood pressure, protein in the urine, and edema (significant swelling) during pregnancy. About 5% of women with preeclampsia progress to eclampsia, a significant cause of maternal and fetal death. Eclampsia is characterized by seizures, in addition to high blood pressure and increased risk of hemorrhage (severe bleeding) (25). A study in 154 pregnant women at increased risk of preeclampsia found that those who were riboflavin deficient were 4.7 times more likely to develop preeclampsia than those who had adequate riboflavin nutritional status (26). The cause of preeclampsia-eclampsia is not known. Decreased intracellular levels of flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress, and interfere with nitric oxide release and thus blood vessel dilation – all of these changes have been associated with preeclampsia (26).

A 2015 meta-analysis of 54 case-control studies found that the *MTHFR* C677T polymorphism was associated with an increased risk of preeclampsia, especially in Caucasian and Asian populations (27). The reduction in the flavoprotein MTHFR activity observed in individuals with the variant *MTHFR* 677TT genotype leads to an increase in plasma homocysteine (14); higher homocysteine concentrations have been associated with preeclampsia (28). One small randomized controlled trial in 450 pregnant women in West Africa, without specified *MTHFR* genotype but at high risk for preeclampsia, found that supplementation with 15 mg of riboflavin daily was not effective in preventing the condition (29), but the study was likely underpowered to detect a significant effect. Further studies are needed to assess the potential benefit of riboflavin supplementation in reducing perinatal complications generally and specifically in preeclamptic women with the *MTHFR* 677TT genotype.

Risk factors for riboflavin deficiency

Alcoholics are at an increased risk of riboflavin deficiency, likely due to decreased dietary intake, decreased absorption, and/or impaired utilization of riboflavin. Interestingly, the elevated blood homocysteine concentrations associated with riboflavin deficiency rapidly decline during alcohol withdrawal (30). Additionally, people with anorexia rarely consume adequate dietary riboflavin, and those who are lactose intolerant are unlikely to meet requirements due to the avoidance of dairy products, the major dietary sources of riboflavin. The conversion of riboflavin into the active cofactor forms FAD and FMN is impaired in hypothyroidism and adrenal insufficiency (3, 4). Further, people who are very active physically (athletes, laborers) may have slightly increased riboflavin requirements. However, riboflavin supplementation has not generally been found to increase exercise tolerance or performance (31) unless the individuals are riboflavin deficient (32).

The Recommended Dietary Allowance (RDA)

The RDA for riboflavin, revised in 1998, is based on the prevention of deficiency (**Table 1**). Clinical signs of deficiency in humans appear at intakes of less than 0.5 to 0.6 milligrams (mg)/day, and urinary excretion of riboflavin is seen at intake levels of approximately 1 mg/day (1).

Table 1. Recommended Dietary Allowance (RDA) for Riboflavin

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.3 (AI)	0.3 (AI)
Infants	7-12 months	0.4 (AI)	0.4 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	0.9	0.9
Adolescents	14-18 years	1.3	1.0
Adults	19 years and older	1.3	1.1
Pregnancy	all ages	-	1.4
Breast-feeding	all ages	-	1.6

Disease Prevention

Cataracts

Age-related cataracts are the leading cause of visual disability in the US and other developed countries. Research has focused on the role of nutritional antioxidants because of evidence that light-induced oxidative damage of lens proteins may lead to the development of age-related cataracts. A case-control study found significantly decreased risk of age-related cataracts (33% to 51%) in men and women in the highest quintile of dietary riboflavin intake (median of 1.6 to 2.2 mg/day) compared to those in the lowest quintile (median of 0.08 mg/day in both men and women) (33). Another case-control study reported that individuals in the highest quintile of riboflavin status, as measured by red blood cell glutathione reductase activity, had approximately one-half the occurrence of age-related cataract as those in the lowest quintile of riboflavin status, though the results were not statistically significant (34). A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of riboflavin intake were 50% less likely to have cataracts than those in the lowest quintile (35). A prospective cohort study of more than 50,000 women did not observe a difference between rates of cataract extraction between women in the highest quintile of riboflavin intake (median of 1.5 mg/day) and women in the lowest quintile (median of 1.2 mg/day) (36). However, the range between the highest and lowest quintiles was small, and median intake levels for both quintiles were above the RDA for riboflavin. A study in 408 women found that higher dietary intakes of riboflavin were inversely associated with a five-year change in lens opacification (37). A randomized controlled trial using a fractional factorial design showed that compared with placebo, the combined supplementation with riboflavin (3 mg/day) and niacin (40 mg/day) for five to six years reduced the prevalence of nuclear cataract but increased the progression of posterior subcapsular cataracts in population affected by multiple nutrient deficiency living in rural China (38). Of note is that the results of this trial are somewhat conflicting, and the study design does not allow the effects of riboflavin and niacin to be differentiated. In summary, there is some evidence predominantly from observational studies, that suggests higher riboflavin status might be beneficial; however, more evidence from well-designed, randomized controlled trials is needed to confirm a role for riboflavin in the prevention of cataracts.

Cancer

The flavoprotein, methylenetetrahydrofolate reductase (MTHFR), plays a pivotal role in folate-mediated one-carbon metabolism. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the cofactor form necessary for the re-methylation of homocysteine to methionine (see **Figure 2** above). The conversion of homocysteine to methionine is of importance for homocysteine detoxification and for the production of S-adenosylmethionine (SAM), the methyl donor for the methylation of DNA and histones. Folate deficiency and elevated homocysteine concentrations may increase cancer risk (see the article on Folate). Aberrant methylation changes are also known to alter the structure and function of DNA and histones during cancer development (39). Since MTHFR controls the detoxification of homocysteine and the supply of methyl groups for SAM synthesis, a reduction in its activity can affect homocysteine metabolism and disturb cellular methylation processes. The substitution of a cytosine by a thymine in position 677 (c.677C>T) in the *MTHFR* gene is a polymorphism that affects the binding of FAD and leads to an increased propensity for MTHFR to lose its flavin coenzyme (40). Subjects homozygous for this mutation (*MTHFR* 677TT genotype) exhibit reduced MTHFR activity and increased risk for a wide variety of cancers (41-43), but the evidence of an association between this polymorphism and cancer is inconsistent, with some reports suggesting a reduction in colorectal cancer risk with the T allele (44).

As mentioned above (see B-complex vitamins), riboflavin intake is a determinant of homocysteine concentration. This suggests that riboflavin status can influence MTHFR activity and the metabolism of folate, thereby affecting cancer risk (43). In a randomized, double-blind, placebo-controlled study, 93 subjects with colorectal polyps and 86 healthy subjects were given a placebo, folic acid (400 or 1,200 μg/day), or folic acid (400 μg/day) plus riboflavin (5 mg/day) for 45 days. These interventions significantly improved folate and riboflavin status in vitamin-supplemented individuals compared to those taking the placebo. Interestingly, riboflavin enhanced the effect of 400 μg folic acid on circulating 5-methyltetrahydrofolate (5-MTHF) specifically in the polyp patients with the C677T genetic variant (45). This suggests that riboflavin may improve the response to folic acid supplementation in individuals with a reduced MTHFR activity. Additionally, a prospective cohort study of 88,045 postmenopausal women found total (dietary plus supplemental) intake of riboflavin to be inversely correlated with colorectal cancer risk when comparing the highest (>3.97 mg) and lowest (<1.80 mg) quartiles of daily intake (46); intake in the reference group was well above the RDA for riboflavin of 1.1 mg/day. The subjects in this study were not prescreened to identify those with the variant *MTHFR* 677TT genotype, and the association between this polymorphism and colorectal cancer remains unclear, with some reports suggesting a reduction in cancer risk with the T allele (44). Two meta-analyses have found inverse associations between riboflavin intake and risk of colorectal cancer (47, 48). The most recent of these was a dose-response meta-analysis that pooled results from five prospective cohort studies, nine case-control studies, and two studies reporting blood concentrations of riboflavin. This analysis found that higher intakes of riboflavin were associated with a significantly lower risk of colorectal cancer (RR=0.87; 95% CI, 0.81-0.93); inverse associations were observed for both dietary riboflavin intake and total daily intake from the diet and supplements (48).

Associations between riboflavin intake and cancer risk have also been evaluated in other types of cancer. A seven-year intervention study evaluated the use of riboflavin-fortified salt in 22,093 individuals at high risk for esophageal cancer in China. Riboflavin status and esophageal pathology (percent normal, dysplastic, and cancerous tissues) improved in the intervention group compared to the control group, but the lower incidence of esophageal cancer found in the intervention group was not statistically significant (49). Additionally, a 25-year follow up of an intervention trial in patients at high risk for gastric cancer found that dietary supplementation with riboflavin (3.2 mg/day) and niacin (40 mg/day) for five years decreased the risk of mortality from esophageal cancer by 8% but had no effect on mortality from gastric cancer (50). In the Melbourne Collaborative Cohort Study, which followed 41,514 men and women over a 15-year period, weak inverse associations were found between riboflavin intake and lung cancer (51) and breast cancer (52); no association of riboflavin intake with prostate cancer was observed in this cohort (53). A 2017 meta-analysis of 10 observational studies found an overall inverse association of riboflavin intake and breast cancer incidence and reported a 6% lower risk with each 1 mg/day increment of riboflavin intake (54). Further, studies to date have not found riboflavin intake or measures of riboflavin status to be associated with renal cell carcinoma, as reviewed in a recent meta-analysis (55).

Disease Treatment

Migraine headaches

Some evidence indicates that impaired mitochondrial oxygen metabolism in the brain may play a role in the pathology of migraine headaches. Since riboflavin is the precursor of the two flavocoenzymes (FAD and FMN) required by the flavoproteins of the mitochondrial electron transport chain, supplemental riboflavin has been investigated as a treatment for migraine. A randomized controlled trial examined the effect of very high dose riboflavin (400 mg/day) for three months on migraine prevention in 54 men and women with a history of recurrent migraine headaches (56). Riboflavin compared to placebo reduced attack frequency and the number of headache days, though the beneficial effect was most pronounced during the third month of treatment (56). Another study by the same investigators found that treatment with either a β-blocker drug or high-dose riboflavin (400 mg/day) for four months resulted in clinical improvement, but each therapy appeared to act on a distinct pathological mechanism: β-blockers on abnormal cortical information processing and riboflavin on decreased brain mitochondrial energy reserve (57). A small study in 23 patients reported a reduction in median migraine attack frequency after supplementation with 400 mg of riboflavin daily for three months (58). A single-blinded, randomized, parallel group trial in 85 patients with migraine headaches (ages 15-55 years), high-dose riboflavin supplementation (400 mg/day) for 12 weeks decreased migraine frequency, duration, and severity compared to baseline and was as effective as sodium valproate (500 mg/day) (59), a medication with established efficacy in migraine preventative therapy (60). Riboflavin elicited significantly fewer adverse effects compared to the drug (59). Thus, although the available trials have been small and short term, most studies to date suggest that high-dose riboflavin supplementation might be a useful adjunct therapy in adults with migraine headaches.

A few randomized controlled trials have investigated the effect of riboflavin supplementation on the frequency and severity of headache attacks in children with migraines. An initial study evaluated riboflavin at 200 mg/day for 12 weeks in 48 children of ages 5 to 15 years old (61). A second study was a cross-over trial with half of the 42 children, ages 6 to 13, receiving 50 mg/day riboflavin for 16 weeks then placebo (100 mg/day carotene) for 16 weeks (with a four-week washout period in between each), while the other half were first given the placebo then riboflavin (62). Neither study showed differences in the frequency, duration, or intensity of migraines between treatments. However, a more recent trial found a benefit of intervention with higher dose riboflavin: children with migraine treated with 400 mg/day of riboflavin for 12 weeks (n=30) had reductions in migraine frequency and duration, but not intensity, compared to placebo (n=30), yet no benefit was seen in children taking 200 mg/day for 12 weeks in this study (63). Additionally, a randomized controlled trial in 98 adolescents, ages 12 to 19 years, found that 400 mg/day of riboflavin for three months decreased both headache frequency and duration and improved migraine-related disability compared to placebo (64). Retrospective studies of children and adolescents suffering from migraine have also suggested some benefit associated with supplemental riboflavin (65-67). Thus, studies to date are somewhat conflicting, and more research is needed to understand whether riboflavin supplementation might have utility in the treatment of childhood migraine and the most effective dose required for any beneficial effects.

Metabolic disorders

Increasing evidence from case reports indicates that patients with autosomal recessive disorders caused by defective FAD-dependent enzymes could benefit from riboflavin supplementation.

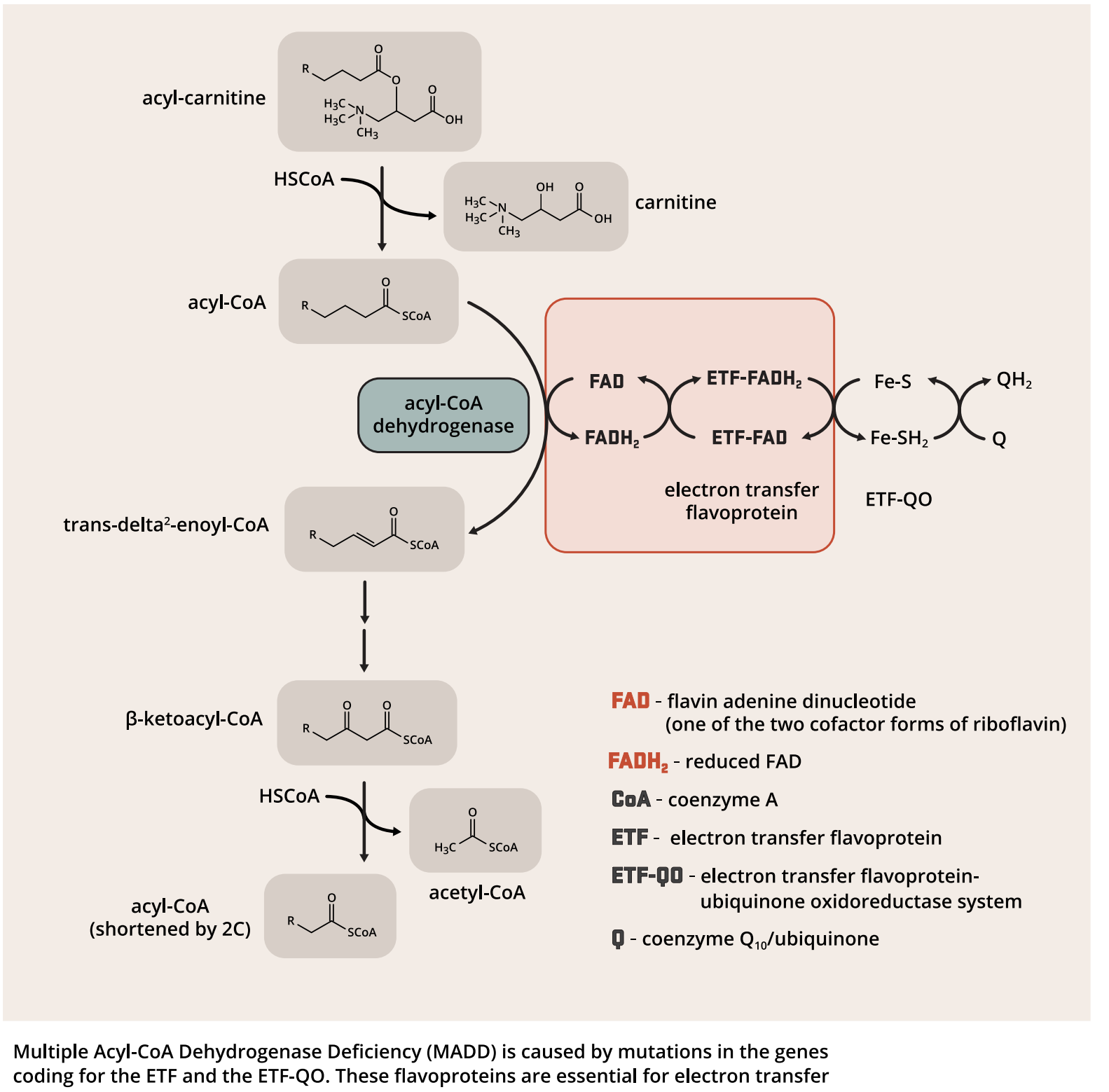
Multiple acyl-CoA dehydrogenase deficiency (MADD)

MADD, also known as type II glutaric aciduria (or acidemia), is a fatty acid metabolism disorder characterized by the accumulation of short-, medium-, and long-chain acyl-carnitines in various tissues. MADD is classified into three separate types based on age of onset and clinical symptoms: type I MADD is evident in the neonatal period and is characterized by the presence of congenital anomalies; type II MADD is present in the neonatal period but lacks congenital defects; and type III is characterized by late onset, from infancy through adulthood (68), and even as late as the seventh decade of life (69). Clinical symptoms of type I and II MADD present shortly after birth and include hypoglycemia, hyperammonemia, metabolic acidosis, hepatomegaly, and respiratory distress (68, 70); these forms of MADD are often fatal in infancy, even if treated. Type III MADD usually presents later in life and includes milder symptoms, varying from periodic vomiting, rhabdomyolysis, muscle pain and weakness, and exercise intolerance (68, 70). Peripheral neuropathy has also recently been reported as a symptom of adult-onset MADD (71).

MADD is caused by autosomal recessive mutations in genes that impair the activity of enzymes involved in the transfer of electrons from acyl-coenzyme A (acyl-CoA) to coenzyme Q$_{10}$/ubiquinone inside the mitochondria (**Figure 3**). *ETFA*, *ETFB*, and *ETFDH* code for the two subunits of the electron transfer flavoprotein (ETF-A and -B) and for ETF dehydrogenase/ubiquinone oxidoreductase (ETFDH/ETFQO), respectively. Deficiencies in these enzymes (ETF or ETFDH) lead to a decrease in oxidized FAD, which becomes unavailable for FAD-dependent dehydrogenation reactions, including the first step in β-oxidation – a major fatty acid catabolic process that takes place in the mitochondria. A defect in fatty acid β-oxidation causes lipid accumulation in skeletal muscles, leading to lipid storage myopathy characterized by muscle pain and weakness and exercise intolerance.

Together with a low-fat, high-carbohydrate diet, riboflavin supplementation has led to significant clinical improvements in patients with *ETFDH* mutations. The specific type of the mutation in *ETF*/*ETFDH* contributes to age of onset, severity, and responsiveness to riboflavin treatment (70, 72). Additionally, the report of a 20-year-old man with riboflavin-responsive MADD failed to find mutations in *ETF* and *ETFDH* genes, suggesting that other sites of mutation should not be excluded (73). Finally, secondary deficiencies in the respiratory chain are observed in MADD and appear to respond favorably to riboflavin supplementation (72, 74).

Figure 3. Fatty Acid β-Oxidation and the Electron Transfer Flavoprotein System



acyl-carnitine
HSCoA
carnitine
acyl-CoA
acyl-CoA dehydrogenase
FAD
FADH₂
ETF-FADH₂
ETF-FAD
electron transfer flavoprotein
Fe-S
Fe-SH₂
QH₂
Q
ETF-QO
trans-delta²-enoyl-CoA
β-ketoacyl-CoA
HSCoA
acetyl-CoA
acyl-CoA (shortened by 2C)
FAD - flavin adenine dinucleotide (one of the two cofactor forms of riboflavin)
FADH₂ - reduced FAD
CoA - coenzyme A
ETF - electron transfer flavoprotein
ETF-QO - electron transfer flavoprotein-ubiquinone oxidoreductase system
Q - coenzyme Q₁₀/ubiquinone

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is caused by mutations in the genes coding for the ETF and the ETF-QO. These flavoproteins are essential for electron transfer from the fatty acid β-oxidation pathway to the respiratory chain.

Acyl-CoA dehydrogenase 9 deficiency (ACAD9)

Acyl-CoA dehydrogenase family member 9 (ACAD9) is an FAD-dependent enzyme with important roles in both the electron transport chain and β-oxidation of fatty acids in the mitochondria. Recessive mutations in the *ACAD9* gene coding for ACAD9 have been found in patients with mitochondrial complex I deficiency, a respiratory chain disorder (75). Complex I carries electrons from NADH to coenzyme Q$_{10}$ in the electron transport chain. Defective oxidative phosphorylation (ATP synthesis by the respiratory chain) due to complex I deficiency has been linked to a broad variety of clinical manifestations, from neonatal death to late-onset neurodegenerative diseases. The clinical symptoms of complex I deficiency due to *ACAD9* mutations typically include muscle weakness, exercise intolerance, lactic acidosis, and hypertrophic cardiomyopathy (76). However, symptoms can be of varying severity, likely due to the remaining functional activity of ACAD9. For example, affected patients have been reported to exhibit a spectrum of cardiac deficits, including isolated, mild ventricular hypertrophy to severe hypertrophic cardiomyopathy (77).

Riboflavin supplementation (100-300 mg/day) has been shown to increase complex I activity in patients with childhood-onset clinical forms of ACAD9 deficiency. Improvements in muscle strength and exercise tolerance have also been associated with riboflavin supplementation (78-80). A review of cases of ACAD9 deficiency presenting in infancy (i.e., cases with severe symptoms) found riboflavin treatment to be associated with improved survival: 7 of 22 patients treated with riboflavin succumbed to the illness compared to 16 out of 17 untreated patients (76).

Defective riboflavin transport-associated disorders

SLC52A1, *SLC52A2*, and *SLC52A3* genes code for the human riboflavin transporters RFVT1, RFVT2, and RFVT3, respectively. Mutations in these genes lead to riboflavin transporter deficiency, a rare neurodegenerative condition with variable age of onset, from infancy to early stages of adulthood. Autosomal recessive mutations in *SLC52A2* or *SLC52A3* respectively cause disorders known as riboflavin transporter deficiency type 2 (RFVT2 deficiency) and riboflavin transporter deficiency type 3 (RFVT3 deficiency). These genetic disorders were formerly called Brown-Vialetto-Van Laere syndrome and Fazio-Londe syndrome (81). Riboflavin transporter deficiency caused by mutation of *SLC52A1* is exceedingly rare and has been reported in only three cases (reviewed in 82).

Clinical features of riboflavin transporter deficiency can include muscle weakness in the arms and legs, sensory ataxia, bulbar palsy with hypotonia and facial weakness, sensorineural deafness, and respiratory insufficiency (83, 84). High-dose, oral supplementation with riboflavin improves many of these symptoms in the majority of affected patients; such treatment should be given at the time of suspected riboflavin transporter deficiency for a better prognosis (84). A 2016 review of the published literature found that oral supplementation with riboflavin – at doses ranging from 7 to 60 mg/kg/day – led to improved symptoms in 71% of the patients (n=39) and to no deaths (83). In contrast, all of the untreated patients (n=31) had a progression of the disease and a mortality rate of at least 48% (83).

Riboflavin-responsive trimethylaminuria

Primary trimethylaminuria is caused by defective oxidation of trimethylamine by a liver flavoprotein called flavin containing mono-oxygenase 3 (FMO3). Individuals with FMO3 deficiency have increased levels of trimethylamine in urine, sweat, and breath (85). This socially distressing condition is known as "fish odor syndrome" due to the fishy odor and volatile nature of trimethylamine. *FMO3* gene mutations are usually associated with mild or intermittent trimethylaminuria; the condition is sometimes limited to peri-menstrual periods in female subjects or to the consumption of trimethylamine-rich food. The clinical management of the condition includes dietary restriction of trimethylamine and its precursors, such as foods rich in choline and seafood, as well as cruciferous vegetables that contain both trimethylamine precursors and FMO3 antagonists (86). The use of riboflavin supplements was reported in a 17-year-old female patient affected by pyridoxine non-responsive homocystinuria (87). The disease was initially treated with betaine (a choline derivative), which caused body odor secondary to FMO3 deficiency. Riboflavin supplementation (200 mg/day) reduced trimethylamine excretion and the betaine treatment-related body odor. Similar effects were seen with riboflavin supplementation in two pediatric patients (88). The data suggest that riboflavin might help maximize residual FMO3 enzyme activity in patients with primary trimethylaminuria. Moreover, a recent case report in a 35-year-old male with HIV described supplemental riboflavin as an effective treatment for secondary trimethylaminuria caused by antiretroviral therapy (89).

Hypertension

Hypertension in adulthood is recognized as the leading risk factor contributing to mortality worldwide primarily from cardiovascular disease, while hypertension in pregnancy leads to serious adverse fetal and maternal outcomes. A number of risk factors are recognized to contribute to the development of hypertension. In recent years, evidence has emerged from genetic and clinical studies pointing to the role of one-carbon metabolism in blood pressure (90). The common *MTHFR* C677T polymorphism, affecting 1 in 10 adults globally, is associated with higher blood pressure, although this is much less well recognized compared with the phenotype of elevated homocysteine concentrations that was established at the time of discovery of this polymorphism and its link with cardiovascular disease (91). Meta-analyses show that this polymorphism is associated with an increased risk of hypertension by up to 87% and of heart disease and stroke by up to 40% (92). The *MTHFR* C677T polymorphism is also associated with a significantly higher risk of hypertension in pregnancy (93) and with preeclampsia (27).

Since FAD is required as a cofactor for the MTHFR enzyme and the *MTHFR* C677T polymorphism results in decreased MTHFR activity, studies have investigated whether affected individuals may benefit from riboflavin supplementation. In an initial randomized controlled trial in 77 healthy young adults stratified by *MTHFR* genotype, riboflavin supplementation at dietary levels (1.6 mg/day for 12 weeks) resulted in marked lowering of homocysteine concentrations in the *MTHFR* 677TT genotype group, but not in the 677CC or 677CT genotype groups who exhibited normal plasma homocysteine at baseline (15). Three randomized controlled trials subsequently investigated the effect of riboflavin on blood pressure in patients with hypertension with or without overt cardiovascular disease (91, 94, 95). The results of these trials showed that supplementation with low-dose riboflavin (1.6 mg/day for 16 weeks) resulted in significant lowering of blood pressure and reduction in incidence of hypertension specifically in those patients with the variant *MTHFR* 677TT genotype. Riboflavin intervention reduced mean systolic/diastolic blood pressure in those with the TT genotype from 144/87 to 131/80 mm Hg, with no response observed in those without the genetic variant (i.e., the CT or CC genotypes) (89). Notably, the 13 mm Hg decrease in systolic blood pressure occurred even though over 80% of the patients were taking one or more antihypertensive drugs at recruitment, and the addition of supplemental riboflavin was shown to greatly enhance the achievement of goal blood pressure with routine antihypertensive drugs (89, 91). Furthermore, the magnitude of blood pressure response achieved with riboflavin in these trials compares very favorably with typical decreases from other interventions, such as dietary salt reductions of 3 g/day (3.6/1.9 mm Hg) and 6 g/day (7.1/3.9 mm Hg). The trial findings therefore suggest that the excess risk of hypertension linked to this genetic polymorphism can be overcome by low-dose riboflavin supplementation. Also, analysis of plasma samples from individuals participating in these trials showed lower concentrations of S-adenosylmethionine (SAM), an important methyl group donor for methylation reactions, in those with the *MTHFR* 677TT genotype versus the CC genotype (96). However, riboflavin supplementation (1.6 mg/day) for 12 weeks was shown to increase plasma concentrations of SAM and another one-carbon metabolite, cystathionine (96), and thus may have potential in correcting the altered one-carbon metabolism arising with the variant TT genotype.

Thus, studies to date indicate that riboflavin supplementation may have benefits in lowering blood pressure and reducing hypertension in individuals (and sub-populations) affected by the common *MTHFR* C677T polymorphism. However, the mechanisms explaining the blood pressure phenotype and its responsiveness to riboflavin remain unclear. Future studies examining the effects of riboflavin supplementation on one-carbon metabolism may help to elucidate the biological mechanisms involved. Interestingly, a recent randomized controlled trial found that riboflavin supplementation in those with the variant *MTHFR* 677TT genotype resulted in altered DNA methylation of certain genes known to be involved in blood pressure regulation (97).

Cancer

Anticancer agents often display various side effects that may force patients to limit the dose or to discontinue the treatment. The antioxidant effect of co-administering riboflavin (10 mg/day), niacin (50 mg/day), and coenzyme Q$_{10}$ (100 mg/day) was evaluated in 78 postmenopausal patients with breast cancer treated with tamoxifen for 90 days. This supplementation effectively prevented the oxidative stress associated with tamoxifen treatment (98).

Riboflavin can also act as a photosensitizer, and this property may have value in photodynamic therapy of cancer. A mouse model was used to assess the effect of riboflavin in combination with cisplatin, one of the most effective anticancer agents. Under light exposure, riboflavin administration reduced cisplatin-induced DNA damage in the liver and kidneys (99). These results are promising, but human studies are needed to examine whether riboflavin is an effective adjunct to chemotherapy.

Corneal disorders

Corneal ectasia is an eye condition characterized by irregularities of the cornea that affect vision. Corneal cross-linking – a fairly new procedure used by professionals to limit the progression of corneal damage –involves the use of topical riboflavin in conjunction with ultraviolet-A irradiation. Riboflavin functions as a photosensitizer in the reaction. Cross-linking modifies the properties of the cornea and strengthens its architecture (100, 101).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of unknown etiology that is characterized by the progressive destruction of myelin and nerve fibers in the central nervous system, causing neurological symptoms in affected individuals (102). Riboflavin appears to have a role in the formation of myelin (103), and oxidative stress has been implicated in the pathogenesis of MS; thus, riboflavin may be helpful in treatment of the disease. A strong inverse association between dietary riboflavin intake and risk for MS was initially observed in a case-control study (104). In a mouse model of MS (i.e., experimental autoimmune encephalomyelitis), riboflavin supplementation improved clinical measures of the disease (105). However, a randomized, double-blind, placebo-controlled pilot study in 29 patients with MS found that supplementation with 10 mg/day of riboflavin for six months had no effect on MS-related disability, assessed by the Expanded Disability Status Scale (106). Large-scale randomized, placebo-controlled trials are needed to determine whether riboflavin supplementation has a beneficial effect in the treatment of MS.

Sources

Food sources

Most plant- and animal-derived foods contain at least small quantities of riboflavin. In the US, wheat flour and bread have been enriched with riboflavin (as well as thiamin, niacin, and iron) since 1943. Data from a US national survey indicate that the average dietary intake of riboflavin is 2.5 mg/day for men and 1.8 mg/day for women (107); these intakes are well above the RDA values of 1.3 mg/day for men and 1.1 mg/day for women. Surveys of adults of ages 70 years or older showed similar intakes: 2.2 mg/day for older men and 1.8 mg day for older women (107).

Riboflavin is heat-stable, but it is easily destroyed upon exposure to light. For instance, up to 50% of the riboflavin in milk contained in a clear glass bottle can be destroyed after two hours of exposure to bright sunlight 6. Nationally representative surveys from the US, Ireland, and the UK showed that milk and other dairy products were the main dietary contributors to riboflavin intake, followed by meat and ready-to-eat breakfast cereals (108-110). Some foods with substantial amounts of riboflavin are listed in **Table 2**, along with their riboflavin content in milligrams (mg). For more information on the nutrient content of food, search USDA's FoodData Central.

The bioavailability of riboflavin from food is reported to be very high, nearly 95% (108). Limited data exist for the relative bioavailability of riboflavin from different food sources, however a cross-over study in healthy women using stable isotopes and kinetic modeling did not find significant differences in riboflavin absorption from milk and spinach (111).

Table 2. Some Food Sources of Riboflavin

Food	Serving	Riboflavin (mg)
Fortified breakfast wheat, puffed cereal	1 cup	0.22
Milk (low-fat, 1%)	1 cup	0.42
Cheddar cheese	1 ounce	0.12
Egg (cooked, hard-boiled)	1 large	0.26
Almonds, unsalted	1 ounce	0.33
Salmon (chinook, cooked)	3 ounces*	0.13
Halibut (greenland, cooked, dry-heat)	3 ounces	0.09
Chicken, light meat (roasted)	3 ounces	0.09
Chicken, dark meat (roasted)	3 ounces	0.16
Beef (ground, cooked)	3 ounces	0.16
Broccoli (boiled, chopped)	½ cup	0.10
Asparagus (boiled)	½ cup	0.13
Spinach (boiled)	½ cup	0.21
Bread, whole-wheat	1 slice	0.05
Bread, white (enriched)	1 slice	0.07
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

The most common forms of riboflavin available in supplements are riboflavin and riboflavin 5'-monophosphate. Riboflavin is commonly found in multivitamin and vitamin B-complex preparations (112).

Safety

Toxicity

No toxic or adverse effects of high riboflavin intake in humans are known. Studies in cell culture indicate that excess riboflavin may increase the risk of DNA strand breaks in the presence of chromium (VI), a known carcinogen (113). This may be of concern to workers exposed to chrome, yet no data in humans are available. High-dose riboflavin therapy has been found to intensify urine color to a bright yellow (flavinuria), but this is a harmless side effect. The Food and Nutrition Board did not establish a tolerable upper intake level (UL) when the RDA was revised in 1998 (1).

Drug interactions

Several early reports indicated that women taking high-dose oral contraceptives had diminished riboflavin biomarker status. However, when investigators controlled for dietary riboflavin intake, no differences between users of oral contraceptives and non-users were found (1). Phenothiazine derivatives like the anti-psychotic medication, chlorpromazine (Thorazine), and tricyclic antidepressants inhibit the conversion of riboflavin to FAD and FMN, as do the anti-malarial medication, quinacrine, and the cancer chemotherapy agent, adriamycin (4). Long-term use of the anticonvulsant, phenobarbitol, may increase destruction of riboflavin by liver enzymes, increasing the risk of deficiency (3). Additionally, chronic alcohol consumption has been associated with riboflavin deficiency. In rats chronically fed alcohol, the inhibition of riboflavin transporters caused impairment in intestinal absorption and renal re-uptake of the vitamin (114).

Linus Pauling Institute Recommendation

The RDA for riboflavin (1.3 mg/day for men and 1.1 mg/day for women), which should prevent deficiency in most individuals, is easily met by eating a varied diet. Consuming a varied diet should supply 1.5 mg to 2 mg of riboflavin a day. Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement containing 100% of the Daily Values (DV) will ensure an intake of at least 1.3 mg/day of riboflavin.

Older adults (>50 years)

Some experts in nutrition and aging feel that the RDA (1.3 mg/day for men and 1.1 mg/day for women) leaves little margin for error in people over 50 years of age (115, 116). A study of independently living people between 65 and 90 years of age found that almost 25% consumed less than the recommended riboflavin intake, and 10% had biochemical evidence of deficiency (117). Epidemiological studies of cataract prevalence indicate that riboflavin intakes of 1.6 to 2.2 mg/day may reduce the risk of developing age-related cataracts. Additionally, older people suffering from acute ischemic stroke were found to be deficient for riboflavin (118), and riboflavin deficiency has been linked to a higher risk of fracture in postmenopausal women with the *MTHFR* 677T variant (119). Individuals whose diets may not supply adequate riboflavin, especially those over 50 years of age, should consider taking a multivitamin/mineral supplement, which generally provides at least 1.3 mg/day of riboflavin.

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Thiamin

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Summary

- Thiamin pyrophosphate (TPP), the active form of thiamin, is involved in several enzyme functions associated with the metabolism of carbohydrates, branched-chain amino acids, and fatty acids. *(More information)*
- Severe thiamin deficiency leads to beriberi, a disease that affects multiple organ systems, including the central and peripheral nervous systems. *(More information)*
- Wernicke's encephalopathy refers to an acute neurologic disorder secondary to thiamin deficiency. The Wernicke-Korsakoff syndrome results in persistent alterations in memory formation, along with the encephalopathy-related symptoms. *(More information)*
- Thiamin deficiency can result from poor dietary intake, inadequate provision in parenteral nutrition, reduced gastrointestinal absorption, increased metabolic requirements, or excessive loss of thiamin. Chronic alcohol consumption is the primary cause of thiamin deficiency in industrialized countries. *(More information)*
- Alteration in glucose metabolism has been associated with decreased plasma thiamin concentrations in patients with diabetes. Correction of thiamin deficiency may reduce the risk of vascular complications in these patients. *(More information)*
- Alzheimer's disease has been associated with altered glucose metabolism and thiamin deficiency. Although some promising results have been observed in animal models, it is not known whether supplementation with thiamin or benfotiamine (a synthetic precursor of thiamin) might slow the cognitive decline in patients with Alzheimer's disease. *(More information)*
- A recent study found decreased levels of thiamin in the brain of patients with Huntington's disease. Clinical trials are needed to evaluate whether vitamin supplementation might be a potential therapy. *(More information)*
- Diuretic-induced thiamin excretion may increase the risk of thiamin deficiency and disease severity in subjects with congestive heart failure. Further studies are needed to assess the inclusion of thiamin supplementation in the management of this disease. *(More information)*
- Intravenous thiamin has been studied as potential treatment for sepsis, either as a monotherapy or in combination with other agents like vitamin C and corticosteroids. Large-scale clinical trials are needed to determine its efficacy. *(More information)*

Thiamin (also spelled thiamine) is a water-soluble B vitamin, also known as vitamin B$_1$ or aneurine (1). Isolated and characterized in the 1930s, thiamin was one of the first organic compounds to be recognized as a vitamin (2). Thiamin occurs in the human body as free thiamin and as various phosphorylated forms: thiamin monophosphate (TMP), thiamin triphosphate, adenosine thiamin triphosphate, and thiamin pyrophosphate (TPP), which is also known as thiamin diphosphate.

Function

  - Drug interactions
- LPI Recommendation
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Function

Coenzyme function

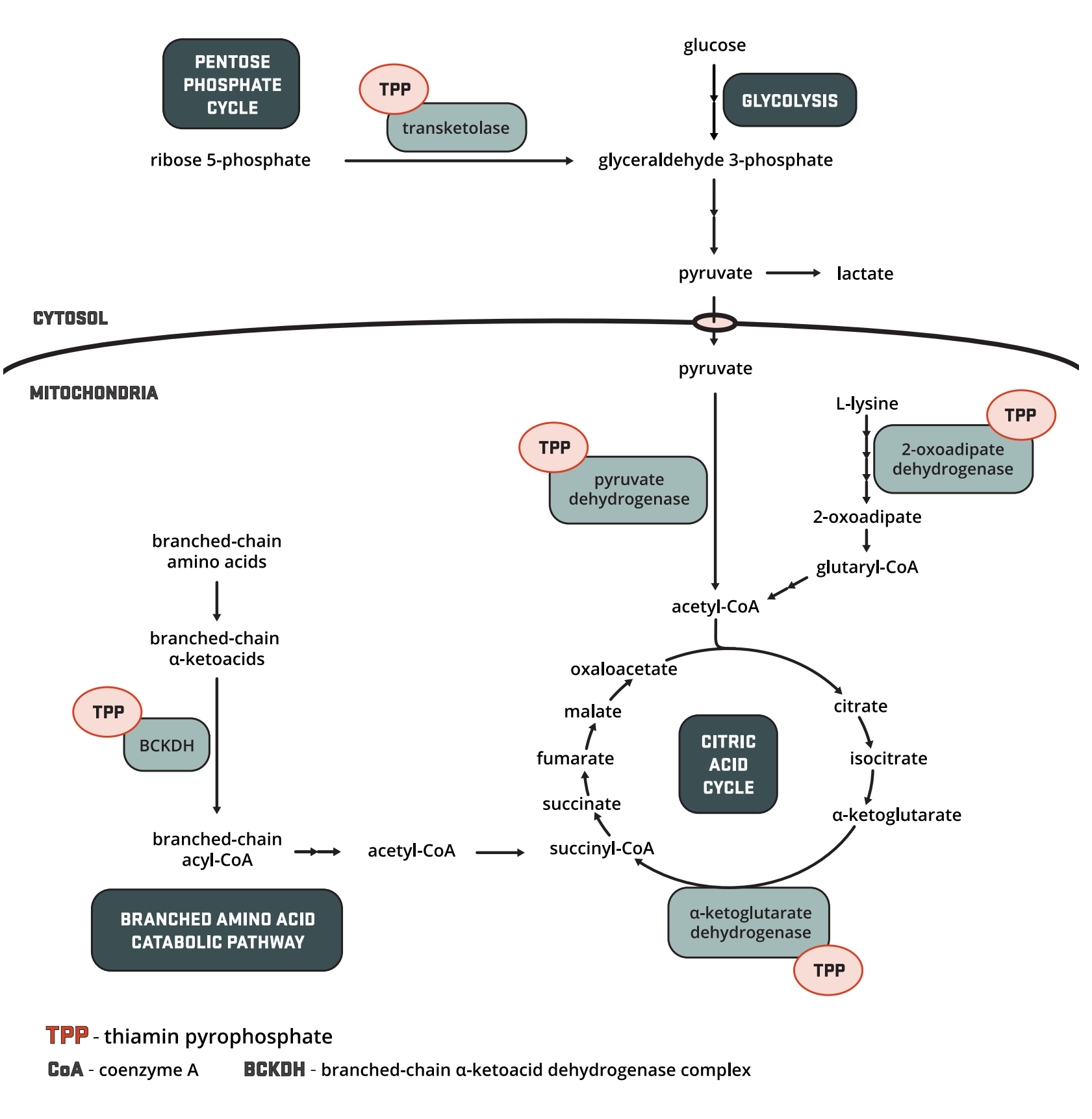
The synthesis of TPP from free thiamin requires magnesium, adenosine triphosphate (ATP), and the enzyme, thiamin pyrophosphokinase. In humans, TPP is required as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. Forms of thiamin are also needed for ribose synthesis and for α-oxidation of 3-methyl-branched fatty acids.

Pyruvate dehydrogenase, **α-ketoglutarate dehydrogenase**, **2-oxoadipate dehydrogenase**, and **branched-chain α-ketoacid dehydrogenase (BCKDH)** each comprise a different enzyme complex found within cellular organelles called mitochondria. They catalyze the decarboxylation of pyruvate, α-ketoglutarate, 2-oxoadipate, and branched-chain amino acids (BCAA) to form acetyl-coenzyme A (CoA), succinyl-CoA, glutaryl-CoA, and derivatives of BCAA, respectively (**Figure 1**). All products play critical roles in the production of energy from food through their connection to the citric acid (Krebs) cycle (2). BCAA, including leucine, isoleucine, and valine, are eventually degraded into acetyl-CoA and succinyl-CoA to fuel the citric acid cycle. The catabolism of the three BCAAs also contributes to the production of cholesterol and donates nitrogen for the synthesis of the neurotransmitters, glutamate and g-aminobutyric acid (GABA) (3). In addition to the thiamin coenzyme (TPP), each dehydrogenase complex requires a niacin-containing coenzyme (NAD), a riboflavin-containing coenzyme (FAD), and lipoic acid.

Transketolase catalyzes critical reactions in another metabolic pathway occurring in the cytosol, known as the pentose phosphate pathway. One of the most important intermediates of this pathway is ribose-5-phosphate, a phosphorylated 5-carbon sugar required for the synthesis of the high-energy ribonucleotides, such as ATP and guanosine triphosphate (GTP). Nucleotides are the building blocks of nucleic acids, DNA, and RNA. The pentose phosphate pathway also supplies various anabolic pathways, including fatty acid synthesis, with the niacin-containing coenzyme NADPH (1, 4). Because transketolase decreases early in thiamin deficiency and, unlike most thiamin-dependent enzymes, is present in red blood cells, measurement of its activity in red blood cells has been used to assess thiamin nutritional status (2, 5, 6).

2-Hydroxyacyl-CoA lyase is a TPP-dependent enzyme in peroxisomes that catalyzes the catabolism of 3-methyl-branched fatty acids through the process of α-oxidation, the oxidative removal of a single carbon atom from fatty acids like phytanic acid (7).

Figure 1. Metabolic Pathways Requiring Thiamin Pyrophosphate (TPP)



Deficiency

Beriberi, the disease resulting from severe thiamin deficiency, was described in Chinese literature as early as 2600 B.C. Thiamin deficiency affects the cardiovascular, muscular, gastrointestinal, and central and peripheral nervous systems (2). Beriberi has been subdivided into dry, wet, cerebral, or gastrointestinal, depending on the systems affected by severe thiamin deficiency (1, 8).

Dry beriberi

The main feature of dry (paralytic or nervous) beriberi is peripheral neuropathy. Early in the course of the neuropathy, "burning feet syndrome" may occur. Other symptoms include abnormal (exaggerated) reflexes, as well as diminished sensation and weakness in the legs and arms. Muscle pain and tenderness and difficulty rising from a squatting position have also been observed (9).

Wet beriberi

In addition to neurologic symptoms, wet (cardiac) beriberi is characterized by cardiovascular manifestations of thiamin deficiency, which include rapid heart rate, enlargement of the heart, severe swelling (edema), difficulty breathing, and ultimately, congestive heart failure. The Japanese literature describes the acute fulminant form of wet beriberi as "shoshin" (10).

Cerebral beriberi

Cerebral beriberi may lead to Wernicke's encephalopathy and Korsakoff's psychosis, especially in people who abuse alcohol. The diagnosis of Wernicke's encephalopathy is based on a "triad" of signs, which include abnormal eye movements, stance and gait ataxia, and cognitive impairment. Due in part to an overlap of symptoms with alcoholic delirium, Wernicke's encephalopathy is thought to be underdiagnosed (11). If left untreated, the irreversible neurologic damage can cause additional clinical manifestations known as Korsakoff's psychosis. This syndrome – also called Korsakoff's dementia, Korsakoff's amnesia, or amnestic confabulatory syndrome – involves a confused, apathetic state and a profound memory disorder, with severe amnesia and loss of recent and working memory.

Thiamin deficiency affecting the central nervous system is referred to as Wernicke's disease when the amnesic state is not present and Wernicke-Korsakoff syndrome (WKS) when the amnesic symptoms are present along with the eye-movement and gait disorders. Rarer neurologic manifestations can include seizures (12). Most WKS sufferers are alcoholics, although it has been observed in other disorders of gross malnutrition, including stomach cancer and AIDS. Administration of intravenous thiamin to WKS patients generally results in prompt improvement of the eye symptoms, but improvements in motor coordination and memory may be less, depending on how long the symptoms have been present. Evidence of increased immune cell activation and increased free radical production in the areas of the brain that are selectively damaged suggests that oxidative stress plays an important role in the neurologic pathology of thiamin deficiency (13).

Gastrointestinal beriberi

TPP is critical for metabolic reactions that utilize glucose in glycolysis and the citric acid cycle (see **Figure 1**). A decrease in the activity of thiamin-dependent enzymes limits the conversion of pyruvate to acetyl-CoA and the utilization of the citric acid cycle, leading to accumulation of pyruvate and lactate. Lactic acidosis, a condition resulting from the accumulation of lactate, is often associated with nausea, vomiting, and severe abdominal pain in a syndrome described as gastrointestinal beriberi (8).

Causes of thiamin deficiency

Thiamin deficiency may result from inadequate thiamin intake, increased requirement for thiamin, excessive loss of thiamin from the body, consumption of anti-thiamin factors in food, or a combination of these factors.

Inadequate intake

Inadequate consumption of thiamin is the main cause of thiamin deficiency in developing countries (2). Thiamin deficiency is common in low-income populations whose diets are high in carbohydrate and low in thiamin (e.g., milled or polished rice). Breast-fed infants whose mothers are thiamin deficient are vulnerable to developing infantile beriberi. Alcoholism, which is associated with low intake of thiamin among other nutrients, is the primary cause of thiamin deficiency in industrialized countries. Some of the non-alcoholic conditions associated with WKS include anorexia nervosa, bariatric surgery (weight-loss surgery), gastrointestinal malignancies, and malabsorption syndromes (14-17). Obese individuals may also be at heightened risk of thiamin deficiency (18, 19). Moreover, cases of Wernicke's encephalopathy have been linked with hyperemesis gravidarum (severe nausea and vomiting during pregnancy) (20, 21), and with parenteral nutrition lacking vitamin supplementation (22, 23).

Increased requirement

Conditions resulting in an increased requirement for thiamin include strenuous physical exertion, fever, pregnancy, breast-feeding, and adolescent growth. Such conditions place individuals with marginal thiamin intake at risk for developing symptomatic thiamin deficiency.

Malaria patients in Southeast Asia were found to be thiamin deficient more frequently than non-infected individuals (24, 25). Malarial infection leads to a large increase in the metabolic demand for glucose. Because thiamin is required for enzymes involved in glucose metabolism, the stresses induced by malarial infection could exacerbate thiamin deficiency in predisposed individuals. HIV-infected individuals, whether or not they had developed AIDS, were also found to be at increased risk for thiamin deficiency (26). Further, chronic alcohol abuse impairs intestinal absorption and utilization of thiamin (1); thus, alcoholics have increased requirements for thiamin. Thiamin deficiency is also observed as a complication of the refeeding syndrome: the introduction of carbohydrates in severely starved individuals leads to an increased demand for thiamin in glycolysis and the citric acid cycle that precipitates thiamin deficiency (27).

Excessive loss

Excessive loss of thiamin may precipitate thiamin deficiency. By increasing urinary flow, diuretics may prevent reabsorption of thiamin by the kidneys and increase its excretion in the urine (28, 29). The risk of thiamin deficiency is increased in diuretic-treated patients with marginal thiamin intake (30) and in individuals receiving long-term, diuretic therapy (31). Individuals with kidney failure requiring hemodialysis lose thiamin at an increased rate and are at risk for thiamin deficiency (32). Alcoholics who maintain a high fluid intake and high urine flow rate may also experience increased loss of thiamin, exacerbating the effects of low thiamin intake (33).

Anti-thiamin factors (ATF)

The presence of anti-thiamin factors (ATF) in foods contributes to the risk of thiamin deficiency. Certain plants contain ATF, which react with thiamin to form an oxidized, inactive product. Consuming very large amounts of tea or coffee (including decaffeinated), as well as chewing tea leaves and betel nuts, might lower thiamin status due to the presence of ATF (34, 35). ATF include mycotoxins (molds) and thiaminases that break down thiamin in food. Individuals who habitually eat certain raw fresh-water fish, raw shellfish, or ferns are at higher risk of thiamin deficiency because these foods contain thiaminase that normally is inactivated by heat in cooking (1, 6). In Nigeria, an acute, neurologic syndrome (seasonal ataxia) has been associated with thiamin deficiency precipitated by a thiaminase in African silkworms, a traditional, high-protein food for some Nigerians (36).

The Recommended Dietary Allowance (RDA)

The RDA for thiamin, revised in 1998 by the Food and Nutrition Board of the Institute of Medicine, was based on the prevention of deficiency in generally healthy individuals (37; **Table 1**).

Table 1. Recommended Dietary Allowance (RDA) for Thiamin

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.2 (AI)	0.2 (AI)
Infants	7-12 months	0.3 (AI)	0.3 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	0.9	0.9
Adolescents	14-18 years	1.2	1.0
Adults	19 years and older	1.2	1.1
Pregnancy	all ages	-	1.4
Breast-feeding	all ages	-	1.4

Disease Prevention

Cataracts

A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of thiamin intake were 40% less likely to have nuclear cataracts than those in the lowest quintile (38). In addition, a study in 408 US women found that higher dietary intakes of thiamin were inversely associated with five-year change in lens opacification (39). However, these cross-sectional associations have yet to be elucidated by studies of causation.

Diabetes mellitus and vascular complications

Patients with diabetes mellitus have been reported to have low plasma concentrations and high renal clearance of thiamin (40, 41), suggesting that individuals with type 1 or type 2 diabetes are at increased risk for thiamin deficiency. Two thiamin transporters, thiamin transporter-1 (THTR-1) and THTR-2, are involved in thiamin uptake by enterocytes in the small intestine and re-uptake in the proximal tubules of the kidneys. One study suggested that hyperglycemia in patients with diabetes could affect thiamin re-uptake by decreasing the expression of thiamin transporters in the kidneys (42). Conversely, thiamin deficiency appears to impair the normal endocrine function of the pancreas and exacerbate hyperglycemia. Early studies showed that insulin synthesis and secretion were altered in the endocrine pancreatic cells of thiamin-deficient rats (43, 44). In humans, thiamin deficiency caused by recessive mutations in the gene encoding THTR-1 leads to diabetes mellitus in the thiamin-responsive megaloblastic anemia syndrome (see Metabolic diseases below).

In a randomized, double-blind pilot study, high-dose thiamin supplements (300 mg/day) were given for six weeks to hyperglycemic individuals (either glucose intolerant or newly diagnosed with type 2 diabetes). Thiamin supplementation prevented any further increase in fasting glucose and insulin concentrations compared with placebo treatment but did not reduce the hyperglycemia (45). However, one study suggested that thiamin supplementation might improve fasting glucose concentrations in in early stages of type 2 diabetes (i.e., pre-diabetes) (46).

Disease Treatment

Alzheimer's disease

Some older adults are at increased risk for developing subclinical thiamin deficiency secondary to poor dietary intake, reduced gastrointestinal absorption, and multiple medical conditions (47, 48). Since thiamin deficiency can result in a form of dementia (Wernicke-Korsakoff syndrome), its relationship to Alzheimer's disease (AD) and other forms of dementia have been investigated. AD is characterized by a decline in cognitive function in elderly people, accompanied by pathologic features that include β-amyloid plaque deposition and neurofibrillary tangles formed by hyperphosphorylated Tau protein (49).

Using positron emission tomography (PET) scanning, reduced glucose metabolism has been observed in brains of AD patients (50). A large, multicenter PET study using a radiolabeled glucose analog, 18F-Fluoro-deoxyglucose (FDG), correlated a reduction in FDG uptake (a surrogate marker for glucose metabolism) with the extent of cognitive impairment in AD patients. This study, which included 822 subjects over 55 years of age that were cognitively normal (n=229), displayed mild cognitive impairment (n=405), or had mild AD (n=188), demonstrated that brain glucose utilization could predict the progression from mild cognitive impairment to AD (51). A nine-year longitudinal study associated the presence of diabetes mellitus in older people (above 55 years old) with an increased risk for developing AD (52). Emerging evidence links type 2 diabetes and AD, conditions that may involve insulin resistance in the brain (reviewed in 53).

A reduction in thiamin-dependent processes in the brain appears to be related to the altered glucose metabolism in patients with AD (54-56). Case-control studies have found blood levels of thiamin, TPP, and TMP to be lower in those with dementia of Alzheimer's type (DAT) compared to control subjects (57, 58). Moreover, several investigators have found evidence of decreased activity of TPP-dependent enzymes, α-ketoglutarate dehydrogenase and transketolase, in the brains of patients who died of AD (59). The finding of decreased brain levels of TPP in the presence of normal levels of free thiamin and TMP suggests altered TPP synthesis rather than poor thiamin bioavailability. However, it is not clear whether the activities of TPP-metabolizing enzymes (including thiamin pyrophoskinase) are altered in AD patients (60, 61). Chronic administration of the thiamin derivative benfotiamine alleviated cognitive alterations and decreased the number of β-amyloid plaques in a mouse model of AD without increasing TMP and TPP levels in the brain. This suggested that the beneficial effects of benfotiamine in the brain were likely mediated by the stimulation of TPP-independent pathways (62). Chronic benfotiamine administration was also shown to decrease the number of neurofibrillary tangles in certain brain regions and improve survival in a mouse model (63). In a rat model of neurodegeneration, long-term oral benfotiamine supplementation increased thiamin pyrophosphate concentrations and led to improvements in insulin signaling and cognitive deficits (64).

Thiamin deficiency has been linked to increased β-amyloid production in cultured neuronal cells and to plaque formation in animal models (65, 66). These pathological hallmarks of AD could be reversed by thiamin supplementation, suggesting that thiamin could be protective in AD. Other disorders, including mitochondrial dysfunction and chronic oxidative stress, have been linked to both thiamin deficiency and AD pathogenesis and progression (13, 55, 67). Presently, there is only slight and inconsistent evidence that thiamin supplements are of benefit in AD. A double-blind, placebo-controlled study of 15 patients (10 completed the study) reported no beneficial effect of 3 grams/day of thiamin on cognitive decline over a 12-month period (68). A preliminary report from another study claimed a mild benefit of 3 to 8 grams of thiamin per day in DAT, but no additional data from that study are available (69). A mild beneficial effect in patients with AD was reported after 12 weeks of treatment with 100 mg/day of a thiamin derivative (thiamin tetrahydrofurfuryl disulfide), but this study was not placebo-controlled (70). A 2001 systematic review of randomized, double-blind, placebo-controlled trials of thiamin in patients with DAT found no evidence that thiamin was a useful treatment for the symptoms of Alzheimer's disease (71). More recently, a small uncontrolled study in five patients with mild-to-moderate AD reported cognitive improvement, measured by the Mini-Mental Status Examination, following supplementation with 300 mg/day of benfotiamine for 18 months (72). In a placebo-controlled study of 70 β-amyloid positive patients with either amnestic mild cognitive impairment (a precursor to AD) or mild AD, those receiving 600 mg/day of benfotiamine for 12 months experienced less cognitive decline compared to placebo, but the differences did not reach statistical significance (p=0.125; 73). Large-scale, randomized controlled trials are needed to determine whether supplemental thiamin or benfotiamine might help slow progression of cognitive decline in those with Alzheimer's disease.

Huntington's disease

Huntington's disease is an inherited neurodegenerative disorder characterized by selective degeneration of nerve cells known as striatal spiny neurons. Symptoms, such as movement disorders and impaired cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. A recent study found decreased levels of the thiamin transporter-2 (THTR-2) protein in the striatum and frontal cortex of patients with Huntington's disease compared to age-and sex-matched healthy controls (74). Compared to control subjects, this study also found lower concentrations of TPP in the striatum and lower concentrations of TMP in the cerebrospinal fluid of patients with Huntington's disease (74). Mutations in the *SLC19A3* gene that encodes THTR-2 causes biotin-thiamin-responsive basal ganglia disease, which is treated with high-dose co-supplementation with biotin and thiamin for life (see Biotin-thiamin-responsive basal ganglia disease below). In a mouse model of Huntington's disease, high-dose supplementation with both of these vitamins improved neuropathological and motor deficits but had no effect on lifespan (p=0.15) (74). A phase II, open-label clinical trial evaluating the effect of combined thiamin-biotin supplementation, at moderate (600 mg/day of thiamin and 150 mg/day of biotin) and high (1,200 mg/day of thiamin and 300 mg/day of biotin) dosages, in Huntington's disease is currently underway (75).

Congestive heart failure

Severe thiamin deficiency (wet beriberi) can lead to impaired cardiac function and ultimately congestive heart failure (CHF). Although cardiac manifestations of beriberi are rarely encountered in industrialized countries, CHF due to other causes is common, especially in the elderly. Loop diuretics used in the treatment of CHF, notably furosemide, increase thiamin excretion, potentially leading to thiamin deficiency (76, 77). Patients with CHF might also have altered thiamin metabolism, including reduced absorption of thiamin in the small intesine (78). A 2015 meta-analysis of nine observational studies found a 2.5 times higher risk of thiamin deficiency in patients with heart failure compared to control subjects (78). As in the general population, older CHF patients were found to be at higher risk of thiamin deficiency than younger ones (79).

An important measure of cardiac function in CHF is the left ventricular ejection fraction (LVEF), which can be assessed by echocardiography. One study in 25 patients found that furosemide use at doses of 80 mg/day or greater was associated with a 98% prevalence of thiamin deficiency (31). In a randomized, double-blind study of 30 CHF patients, all of whom had been taking furosemide (80 mg/day) for at least three months, intravenous (IV) thiamin therapy (200 mg/day) for seven days resulted in an improved LVEF compared to IV placebo (80). When all 30 of the CHF patients in that study subsequently received six weeks of oral thiamin therapy (200 mg/day), the average LVEF improved by 22%. This finding may be relevant because improvements in LVEF have been associated with improved survival in CHF patients (81). However, clinical trials of oral thiamin supplementation in heart failure patients have not found any benefit. In a randomized, double-blind, placebo-controlled trial in 52 patients with systolic heart failure, 300 mg/day of supplemental thiamin for one month did not improve LVEF compared to placebo (82). A randomized, double-blind, placebo-controlled trial in 64 patients with heart failure reported that 200 mg/day or supplemental thiamin for six months did not improve LVEF (83).

Although little evidence supports the routine use of supplemental thiamin in CHF patients, trials specifically in CHF patients with marginal thiamin status have not been done, and some suggest that it may be prudent to screen patients on long-term diuretic therapy for thiamin deficiency and treat accordingly (84).

Type 2 diabetes mellitus and vascular complications

Chronic hyperglycemia in individuals with diabetes mellitus contributes to the pathogenesis of microvascular diseases. Diabetes-related vascular damage can affect the heart (cardiomyopathy), kidneys (nephropathy), retina (retinopathy), and peripheral nervous system (neuropathy). In subjects with diabetes, hyperglycemia alters the function of bone marrow-derived endothelial progenitor cells (EPC) that are critical for the growth of blood vessels (85). Interestingly, a higher daily intake of thiamin from the diet was correlated with more circulating EPC and with better vascular endothelial health in 88 individuals with type 2 diabetes (86). An inverse association has also been found between plasma concentrations of thiamin and the presence of soluble vascular adhesion molecule-1 (sVCAM-1), a marker of vascular dysfunction, in patients with diabetes (40, 87). Early markers of diabetic nephropathy include the presence of serum albumin in the urine, known as microalbuminuria. Administration of thiamin or benfotiamine (a thiamin derivative) prevented the development of renal complications in chemically-induced diabetic rats (88). A randomized, double-blind, placebo-controlled study conducted in 40 patients with type 2 diabetes with microalbuminuria found that high-dose thiamin supplementation (300 mg/day) decreased excretion of urinary albumin over a three-month period (87). Since thiamin treatment has shown promising results in cultured cells and animal models (89-91), the effects of thiamin and its derivatives on vascular complications should be examined in patients with diabetes.

Cancer

Thiamin deficiency and Wernicke-Korsakoff syndrome have been observed in some cancer patients with rapidly growing tumors (92, 93). Research in cell culture and animal models indicates that rapidly dividing cancer cells have a high requirement for thiamin (94). All rapidly dividing cells require nucleic acids at an increased rate, and some cancer cells appear to rely heavily on the TPP-dependent enzyme, transketolase, to provide the ribose-5-phosphate necessary for nucleic acid synthesis. One study found that the levels of THTR-1, transketolase, and TPP mitochondrial transporters were increased in samples of human breast cancer tissue compared to normal tissue, suggesting an adaptation in thiamin homeostasis in support of cancer metabolism (95). Other studies have found that the gene encoding THTR-2 is downregulated in certain cancers (96). Moreover, use of the chemotherapeutic drug, 5-fluorouracil, inhibits phosphorylation of thiamin to thiamin pyrophosphate and may thus lead to thiamin deficiency (97, 98).

Thiamin supplementation in cancer patients is common to prevent thiamin deficiency, but Boros et al. caution that too much thiamin may actually fuel the growth of some malignant tumors (99), suggesting that thiamin supplementation be reserved for those cancer patients who are actually deficient in thiamin. Presently, there is no evidence available from studies in humans to support or refute this theory. However, it would be prudent for individuals with cancer who are considering thiamin supplementation to discuss it with the clinician managing their cancer therapy. Intravenous, high-dose thiamin has been suggested as a treatment for cancer patients with confirmed Wernicke-Korsakoff (93).

Sepsis

Sepsis is a life-threatening critical illness caused by a dysregulated host response to an infection. The widespread inflammation can lead to tissue and organ damage and to death (100). Because thiamin deficiency is common among septic patients (101), several studies have investigated the treatment effect of intravenous thiamin – alone or in combination with other agents like vitamin C and hydrocortisone.

Observational studies examining the association of intravenous thiamin as a monotherapy have mainly looked at its association with lactic acidosis, which commonly occurs in both thiamin deficiency and sepsis, and with mortality. One retrospective study in 123 septic patients and 246 matched controls found that intravenous thiamin administration within 24 hours of hospital admission was linked to improvements in both lactate clearance and 28-day mortality (102). In a small retrospective study of 53 alcohol-use disorder patients presenting with septic shock, lower mortality was observed in the 34 patients who received intravenous thiamin compared to the 19 patients who did not (103).

A few randomized controlled trials have evaluated the effect of intravenous thiamin in the treatment of sepsis. A randomized, double-blind, placebo-controlled trial in 88 patients with sepsis and elevated blood concentrations of lactate reported that intravenous thiamin (200 mg twice daily for seven days or until discharge from the hospital) did not decrease lactate concentrations at 24 hours post initiation of treatment – the primary endpoint of the trial (104). No differences between the treatment and placebo groups were found for the secondary endpoints, which included survival (104). In a subsequent analysis of data from this trial, the septic patients that were given parenteral thiamin (n=31) had lower creatinine concentrations throughout the treatment and were less likely to need renal replacement therapy compared to placebo (n=39; 105).

A 2020 meta-analysis of four studies – one observational and three randomized controlled trials – found no benefit of intravenous thiamin for improving lactate concentrations, length of hospital stay in intensive care, or overall survival (106). Large-scale clinical trials are needed to determine whether parenteral administration of thiamin is beneficial in the treatment of sepsis. Administering thiamin in combination with vitamin C and corticosteroids may be more efficacious to treat sepsis (107); some clinical trials of such treatments are currently underway (see clinicaltrials.gov/).

Metabolic diseases

Thiamin supplementation is included in the clinical management of genetic diseases that affect the metabolism of carbohydrates and branched-chain amino acids (BCAAs).

Thiamin-responsive pyruvate dehydrogenase complex (PDHC) deficiency

Mutations in PDHC prevent the efficient oxidation of carbohydrates in affected individuals. PDHC deficiency is commonly characterized by lactic acidosis, neurologic and neuromuscular degeneration, and death during childhood. The patients who respond to thiamin treatment (from a few mg/day to doses above 1,000 mg/day) exhibit PDHC deficiency due to the decreased affinity of PDHC for TPP (108, 109). Although thiamin supplementation can reduce lactate accumulation and improve the clinical features in thiamin-responsive patients, it does not constitute a cure (110).

Maple syrup urine disease

Inborn errors of BCAA metabolism lead to thiamin-responsive branched-chain ketoaciduria, also known as maple syrup urine disease. Alterations in the BCAA catabolic pathway result in neurologic dysfunction caused by the accumulation of BCAAs and their derivatives, branched-chain ketoacids (BCKA). The therapeutic approach includes a synthetic diet with reduced BCAA content, and thiamin (10-1,000 mg/day) is supplemented to patients with mutations in the E2 subunit of the BCKDH complex (111). In thiamin-responsive individuals, the supplementation has been proven effective to correct the phenotype without recourse to the BCAA restriction diet.

Thiamin-responsive megaloblastic anemia

Mutations in the *SLC19A2* gene that encodes THTR-1 impairs intestinal thiamin uptake and causes thiamin deficiency, leading to thiamin-responsive megaloblastic anemia (112). This syndrome, which is also called thiamin metabolism dysfunction syndrome-1, is characterized by megaloblastic anemia, diabetes mellitus, and deafness. A review of 30 cases reported additional neurologic, visual, and cardiac impairments (113). High-dose oral supplementation with thiamin (up to 300 mg/day) helps to maintain health and correct hyperglycemia in prepubescent children. A recent study in 32 individuals with found no additional benefit of oral doses above 150 mg/day (114). After puberty, a decline in pancreatic function results in the requirement of insulin together with thiamin to control the hyperglycemia. One study also reported that the treatment of a four-month-old girl with 100 mg/day of thiamin did not prevent hearing loss at 20 months of age (115). Early diagnosis of the syndrome and early treatment with thiamin is important for a better prognosis (114).

Biotin-thiamin-responsive basal ganglia disease

Biotin-thiamin-responsive basal ganglia disease (also called biotin-responsive basal ganglia disease, thiamin transporter-2 deficiency, and thiamin metabolism dysfunction syndrome-2) is caused by an autosomal recessive mutation in the *SLC19A3* gene that codes for THTR-2. The disease usually presents around 3 to 10 years of age (116), but an early infantile form of the disease exists with onset as early as one month of age (117). Clinical features include subacute encephalopathy (confusion, drowsiness, altered level of consciousness), ataxia, and seizures.

A retrospective study of 18 affected individuals from the same family or the same tribe in Saudi Arabia showed that biotin monotherapy (5-10 mg/kg/day) efficiently abolished the clinical manifestations of the disease, although one-third of the patients suffered from recurrent acute crises. Often associated with poor outcomes, acute crises were not observed for a five-year follow-up period following thiamin supplementation (300-400 mg/day) – early diagnosis and immediate treatment with biotin and thiamin led to positive outcomes (118). Recent studies have found supplemental thiamin to be important in treating the condition. In an open-label study of 20 pediatric patients with the disease, supplemental thiamin alone was as effective as combined biotin-thiamin supplementation when given for 30 months (119). Lifelong high-dose supplementation with a combination of biotin and thiamin is generally the treatment for biotin-thiamin-responsive basal ganglia disease (116). Early diagnosis and treatment is important to ensure a better prognosis (117, 120).

Other thiamin metabolism dysfunction syndromes

Supplemental thiamin has limited utility in treating other inborn errors of thiamin metabolism. Mutations in the *SLC25A19* gene that codes for the mitochondrial TPP transporter can result in either thiamin metabolism dysfunction syndrome-3 (THMD3) or thiamin metabolism dysfunction syndrome-4 (THMD4). Of these rare syndromes, THMD3 (also called Amish-type microcephaly or Amish lethal microcephaly) has the more severe phenotype, resulting in a congenital microcephaly, elevated concentrations of α-ketoglutarate in urine, and usually death in infancy (121). THMD4 is characterized by episodic encephalopathy and weakness, which often presents following a viral infection or febrile illness in childhood. Some patients affected with THMD4 may respond to high-dose thiamin supplementation (122).

Mutations in the *TPK1* gene result in thiamin pyrophosphokinase 1 deficiency and thiamin metabolism dysfunction syndrome-5 (THMD5), which usually manifests in early childhood. While the clinical presentation of THMD5 varies, affected individuals often experience episodic ataxia, dystonia, and lactic acidosis (123). Only a few cases of THMD5 have been reported to date; two of these patients experienced limited improvement of symptoms upon supplementation with thiamin, in conjunction with adherence to a high-fat diet (124).

Sources

Humans obtain thiamin from dietary sources and from the normal microflora of the colon, although the contribution of the latter towards the body's requirement for thiamin is not clear (125).

Food sources

A varied diet should provide most individuals with adequate thiamin to prevent deficiency. In the US the average dietary thiamin intake for young adult men is about 2 mg/day and 1.2 mg/day for young adult women. A survey of people over the age of 60 found an average dietary thiamin intake of 1.4 mg/day for men and 1.1 mg/day for women (37). However, institutionalization and poverty both increase the likelihood of inadequate thiamin intake in the elderly (126). Whole-grain cereals, legumes (e.g., beans and lentils), nuts, lean pork, and yeast are rich sources of thiamin (1). Because most of the thiamin is lost during the production of white flour and polished (milled) rice, white rice and foods made from white flour (e.g., bread and pasta) are fortified with thiamin in many Western countries. A number of thiamin-rich foods are listed in the table below, along with their thiamin content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Thiamin

Food	Serving	Thiamin (mg)
Lentils (cooked, boiled)	½ cup	0.17
Green peas (cooked, boiled)	½ cup	0.21
Long-grain, brown rice (cooked)	½ cup	0.18
Long-grain, white rice, enriched (cooked)	½ cup	0.13
Long-grain, white rice, unenriched (cooked)	½ cup	0.016
Whole-wheat bread	1 slice	0.13
White bread, enriched	1 slice	0.31
Fortified breakfast cereal (wheat, puffed)	1 cup	0.31
Wheat germ breakfast cereal (toasted, plain)	1 cup	1.88
Pork, lean (loin, tenderloin, cooked, roasted)	3 ounces*	0.80
Pecans	1 ounce (19 halves)	0.19
Spinach (cooked, boiled)	½ cup	0.09
Orange	1 fruit	0.11
Cantaloupe	½ fruit	0.11
Milk	1 cup	0.10
Egg (cooked, hard-boiled)	1 large	0.03
*Three ounces of meat is a serving about the size of a deck of cards		

Supplements

Thiamin is available in dietary supplements and in fortified foods, most commonly as thiamin hydrochloride or thiamin mononitrate (127). Multivitamin supplements typically contain at least 1.2 mg of thiamin, the Daily Value (DV) for adults and children 4 years and older (128).

Benfotiamine is a synthetic, lipid-soluble precursor of thiamin that is available as a dietary supplement. It has higher bioavailability compared to thiamin (129).

Safety

Toxicity

The Food and Nutrition Board did not set a tolerable upper intake level (UL) for thiamin because there are no well-established toxic effects from consumption of excess thiamin in food or through long-term, oral supplementation (up to 200 mg/day). A small number of life-threatening anaphylactic reactions have been observed with large intravenous doses of thiamin (37).

Drug interactions

Reduced blood concentrations of thiamin have been reported in individuals with seizure disorders (epilepsy) taking the anticonvulsant medication, phenytoin, for long periods of time (130). 5-Fluorouracil, a drug used in cancer therapy, inhibits the phosphorylation of thiamin to TPP (131). Diuretics, especially furosemide, may increase the risk of thiamin deficiency in individuals with marginal thiamin intake due to increased urinary excretion of thiamin (29). Moreover, chronic alcohol abuse is associated with thiamin deficiency due to low dietary intake, impaired absorption and utilization, and increased excretion of the vitamin (1). Chronic alcohol feeding to rats showed a decrease in the active absorption of thiamin linked to the inhibition of thiamin membrane transporter THTR-1 in the intestinal epithelium (132). Alcohol consumption in rats also decreases the levels of THTR-1 and THTR-2 in renal epithelial cells, thus limiting thiamin re-uptake by the kidneys (133).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 1.2 mg/day of thiamin for men and 1.1 mg/day for women. A varied diet should provide enough thiamin for most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement, containing 100% of the Daily Values (DV), will ensure an intake of at least 1.5 mg/day of thiamin.

Older adults (>50 years)

Presently, there is no evidence that the requirement for thiamin is increased in older adults, but some studies have found inadequate dietary intake and thiamin insufficiency to be more common in elderly populations (126). Thus, it would be prudent for older adults to take a multivitamin/mineral supplement, which will generally provide at least 1.5 mg/day of thiamin.

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Vitamin A

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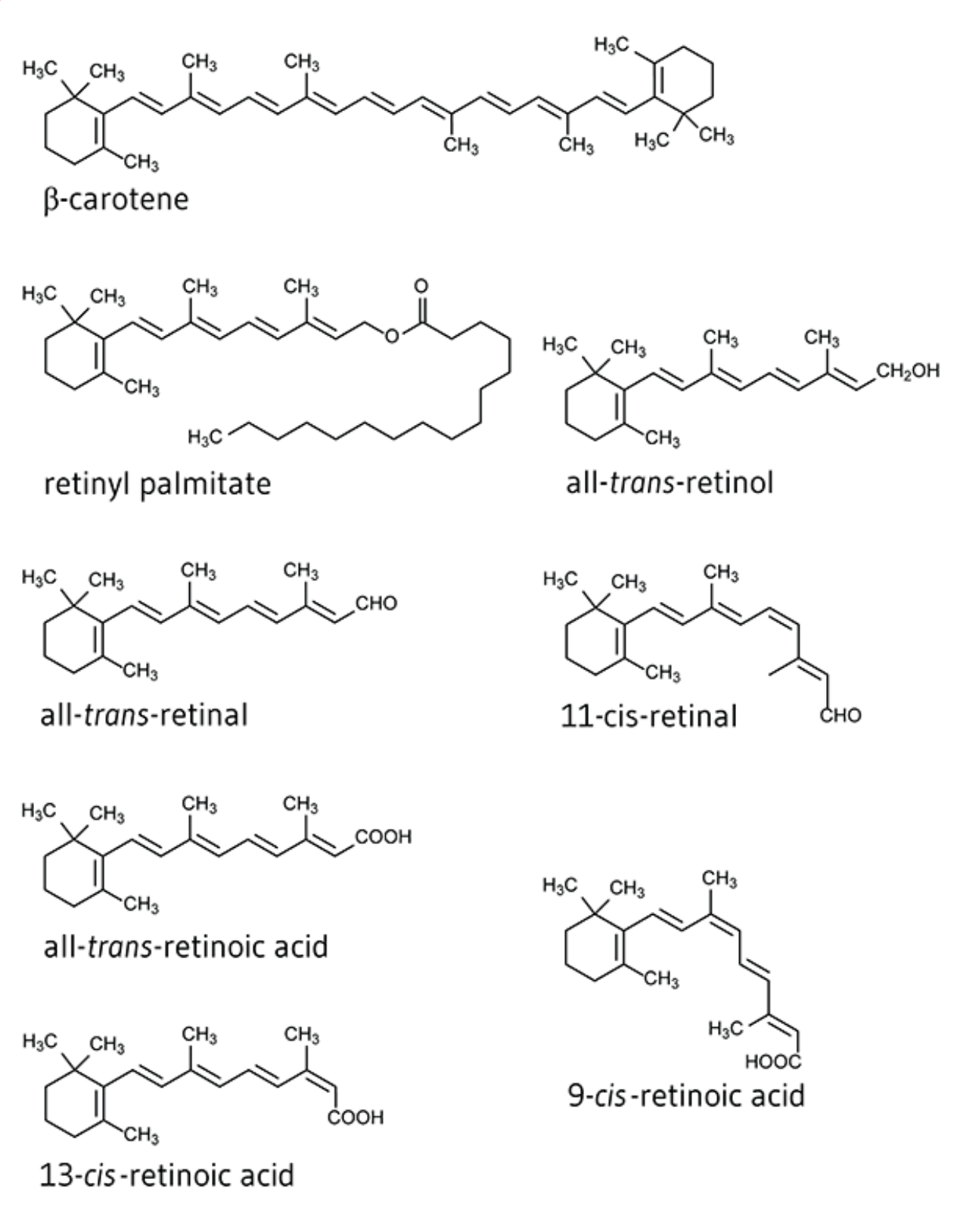
Summary

- Vitamin A is a generic term that refers to fat-soluble compounds found as preformed vitamin A (retinol) in animal products and as provitamin A carotenoids in fruit and vegetables. The three active forms of vitamin A in the body are retinol, retinal, and retinoic acid. *(More information)*
- Vitamin A is involved in regulating the growth and specialization (differentiation) of virtually all cells in the human body. Vitamin A has important roles in embryonic development, organ formation during fetal development, normal immune functions, and eye development and vision. *(More information)*
- Vitamin A deficiency is a major cause of preventable blindness in the world. It is most prevalent among children and women of childbearing age. Vitamin A deficiency is associated with an increased susceptibility to infections, as well as to thyroid and skin disorders. *(More information)*
- The recommended dietary allowance (RDA) is 700 micrograms of retinol activity equivalents (μg RAE)/day for women and 900 μg RAE/day for men. *(More information)*
- Vitamin A prophylaxis appears to significantly reduce childhood mortality in regions at high risk of vitamin A deficiency. Further, high-dose vitamin A supplementation is widely recommended for children over six months of age when they are infected with measles while malnourished, immunodeficient, or are at risk of measles complications. *(More information)*
- Retinoic acid and analogs are used at pharmacological doses in the treatment of acute promyelocytic leukemia and various skin diseases. *(More information)*
- Animal food sources rich in preformed vitamin A include dairy products, liver, and fish oils; fortified cereals may also contain preformed vitamin A. Rich sources of provitamin A carotenoids include orange and green vegetables, such as sweet potato and spinach. *(More information)*
- Overconsumption of preformed vitamin A can be highly toxic and is especially contraindicated prior to and during pregnancy as it can result in severe birth defects. The tolerable upper intake level (UL) for vitamin A in adults is set at 3,000 μg RAE/day. The UL does not apply to vitamin A derived from carotenoids. *(More information)*

Vitamin A is a generic term that encompasses a number of related compounds (**Figure 1**). Retinol and retinyl esters are often referred to as preformed vitamin A. Retinol can be converted by the body to retinal, which can be in turn be oxidized to retinoic acid, the form of vitamin A known to regulate gene transcription. Retinol, retinal, retinoic acid, and related compounds are known as retinoids. β-Carotene and other food carotenoids that can be converted by the body into retinol are referred to as provitamin A carotenoids (see the article on Carotenoids). Hundreds of different carotenoids are synthesized by plants, but only about 10% of them are capable of being converted to retinol (1). The following discussion will focus mainly on preformed vitamin A compounds and retinoic acid.

Figure 1. Chemical Structures



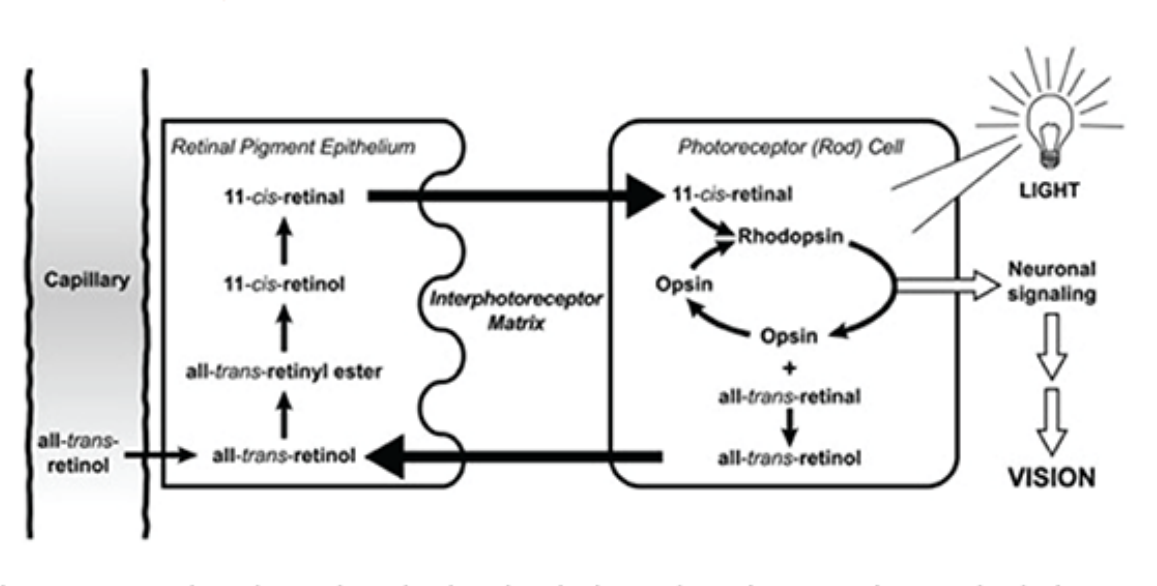
Function

Vitamin A compounds are essential fat-soluble molecules predominantly stored in the liver in the form of retinyl esters (e.g., retinyl palmitate). When appropriate, retinyl esters are hydrolyzed to generate all-*trans*-retinol, which binds to retinol binding protein (RBP) before being released in the bloodstream. The all-*trans*-retinol/RBP complex circulates bound to the protein, transthyretin, which delivers all-*trans*-retinol to peripheral tissues (reviewed in 2). Vitamin A as retinyl esters in chylomicrons was also found to have an appreciable role in delivering vitamin A to extrahepatic tissues, especially in early life (3, 4).

Visual system and eyesight

Located at the back of the eye, the retina contains two main types of light-sensitive receptor cells – known as rod and cone photoreceptor cells. Photons (particles of light) that pass through the lens are sensed by the photoreceptor cells of the retina and converted to nerve impulses (electric signals) for interpretation by the brain. All-*trans*-retinol is transported to the retina via the circulation and accumulates in retinal pigment epithelial (RPE) cells (**Figure 2**) (5). Here, all-*trans*-retinol is esterified to form a retinyl ester, which can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-*cis*-retinol, which can be oxidized to form 11-*cis*-retinal. 11-*cis*-retinal can be shuttled across the interphotoreceptor space to the rod photoreceptor cell that is specialized for vision in low-light conditions and for detection of motion. In rod cells, 11-*cis*-retinal binds to a protein called opsin to form the visual pigment rhodopsin (also known as visual purple). Absorption of a photon of light catalyzes the isomerization of 11-*cis*-retinal to all-*trans*-retinal that is released from the opsin molecule. This photoisomerization triggers a cascade of events, leading to the generation of a nerve impulse conveyed by the optic nerve to the brain's visual cortex. All-*trans*-retinal is converted to all-*trans*-retinol and transported across the interstitial space to the RPE cells, thereby completing the visual cycle.

Figure 2. The Visual Cycle



Retinol is transported to the retina via the circulation, where it moves into retinal pigment epithelial cells. There, retinol is esterified to form a retinyl ester that can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-*cis*-retinol, which can be oxidized to form 11-*cis*-retinal. 11-*cis*-retinal can be shuttled to the rod cell, where it binds to a protein called opsin to form the visual pigment, rhodopsin (also known as visual purple). Absorption of a photon of light catalyzes the isomerization of 11-*cis*-retinal to all-*trans*-retinal and results in its release. This isomerization triggers a cascade of events, leading to the generation of an electrical signal to the optic nerve. The nerve impulse generated by the optic nerve is conveyed to the brain where it can be interpreted as vision. Once released, all-*trans*-retinal is converted to all-*trans*-retinol, which can be transported across the interphotoreceptor matrix to the retinal epithelial cell to complete the visual cycle.

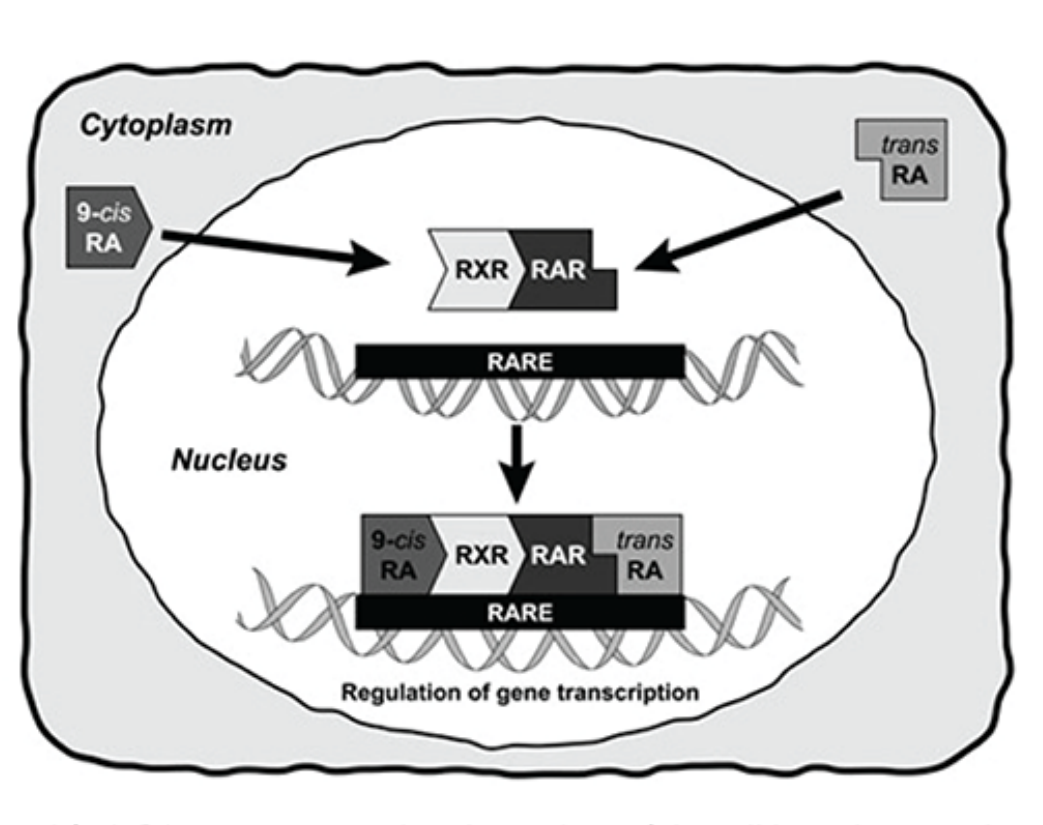
A similar cycle occurs in cone cells that contain red, green, or blue opsin proteins required for the absorption of photons from the visible light spectrum (2). Vitamin A is also essential for mammalian eye development (6). Thus, because vitamin A is required for the normal functioning of the retina, dim-light vision, and color vision, inadequate retinol and retinal available to the retina result in impaired dark adaptation. In the severest cases of vitamin A deficiency, thinning and ulceration of the cornea leads to blindness (see Deficiency).

Regulation of gene expression

Regulatory capacity of retinoic acid

In cells, all-*trans*-retinol can be either stored (in the form of retinyl ester) or oxidized to all-*trans*-retinal by alcohol dehydrogenases. In turn, retinaldehyde dehydrogenases can catalyze the conversion of all-*trans*-retinal into two biologically active isomers of retinoic acid (RA): all-*trans*-RA and 9-*cis*-RA. RA isomers act as hormones to affect gene expression and thereby influence numerous physiological processes. All-*trans*-RA and 9-*cis*-RA are transported to the nucleus of the cell bound to cellular retinoic acid-binding proteins (CRABP). Within the nucleus, RA isomers bind to specific nuclear receptor proteins that are ligand-dependent transcription factors (**Figure 3**). Both all-*trans*-RA and 9-*cis*-RA can bind to retinoic acid receptors (RARα, RARβ, and RARγ), whereas only 9-*cis*-RA binds to retinoid X receptors (RXRα, RXRβ, and RXRβ) (7). RAR and RXR subtypes form either complexes of two of the same protein (RAR/RAR and RXR/RXR homodimers) or complexes of two different proteins (RAR/RXR heterodimers). RAR/RXR heterodimers can bind to a regulatory DNA sequence called retinoic acid response element (RARE) located within the promoter of retinoid-responsive genes. The transcriptional activity of RAR/RXR heterodimers appears to be mainly driven by the binding of all-*trans*-RA to RAR.

Figure 3. A Simplified Model of the Regulation of Gene Expression by Retinoic Acid (RA) Isomers



All-*trans*-RA and 9-*cis*-RA are transported to the nucleus of the cell bound to cytoplasmic retinoic acid-binding proteins. Within the nucleus, all-*trans*-RA binds to retinoic acid receptors (RAR) and 9-*cis*-RA binds to retinoid receptors (RXR). RAR and RXR form RAR/RXR heterodimers, which bind to regulatory regions of the chromosome called retinoic acid response elements (RARE). Binding of all-*trans*-RA and 9-*cis*-RA to RAR and RXR respectively allows the complex to regulate the rate of gene transcription.

The activation of RAR by RA binding triggers the recruitment of transcriptional coregulators to target promoters, thereby inhibiting or allowing the transcription of genes (8). RXR also forms heterodimers with several other nuclear receptors, including thyroid hormone receptor (TR), vitamin D receptor (VDR), steroid receptors, and peroxisome proliferator-activated receptor (PPAR) (9). In this way, vitamin A may interact with thyroid hormone, vitamin D, steroids (e.g., estrogen), or PPAR ligands signaling pathways and influence the transcription of a broad range of genes.

There is also evidence that RA/RAR can affect gene expression in a RARE-independent manner. For example, it was reported that RAR could interfere with TGFβ/Smad signaling pathway through direct interaction of RAR with the heterodimeric transcription factor, Smad3/Smad4. In the absence of RA, RAR was found to act as a coactivator of Smad3/Smad4-mediated transcription, while RAR agonists repressed the transcriptional activity of Smad3/Smad4 (10). In retinoblastoma cells, RAR was also involved in RA-induced activation of signaling cascades mediated by tyrosine kinases known as phosphoinositide 3-kinase (PI3K) and leading to cell differentiation (11, 12). RA also appeared to induce neuronal differentiation by activating ERK1/2 MAP kinase signaling pathway that phosphorylated transcription factor, CREB (cyclic AMP response element binding protein). Phosphorylated CREB can subsequently bind to the CREB response element in the promoter of genes involved in cell differentiation (13). Also, independently of RAR, RA was found to inhibit ERK1/2 phosphorylation/activation and subsequent AP1-mediated expression of interleukin-6 in synovial cells (14). Hence, RA can influence the expression of genes whose promoters do not contain RARE.

By regulating the expression of over 500 retinoid-responsive genes (including several genes involved in vitamin A metabolism itself), retinoic acid isomers play major roles in cellular proliferation and differentiation (i.e., cell commitment to highly specialized functions).

Regulatory capacity of retinol

In the eye and tissues like white adipose and muscle, retinol plasma membrane receptor/transporter STRA6 accepts retinol from extracellular RBP and unloads it to intracellular retinol-binding protein (CRBP). STRA6 also cooperates with lecithin:retinol acyltransferase (LRAT), an enzyme that catalyzes retinol esterification and storage, to maintain an inward concentration gradient of retinol (15). Interestingly, retinol uptake by STRA6 was found to trigger the activation of a signaling cascade mediated by tyrosine kinases known as Janus kinases (JAK) and associated transcription factors (STAT). JAK/STAT signaling pathway regulates the expression of a wide range of cytokines, hormones, and growth factors (16). Animal studies have reported that an increased expression of genes, such as *SOCS3* by the JAK/STAT pathway, could result in the inhibition of insulin signaling. Hence, obese mice lacking LRAT or STRA6 appear to be protected from retinol/STRA6-induced insulin resistance (17, 18).

Regulatory capacity of retinal

Apart from its role as a ligand for opsin in the visual cascade (see Visual system and eyesight), retinal has been specifically implicated in the regulation of genes important for lipid metabolism. In humans, two types of adipose tissue have been distinguished based on their respective functions: white adipose tissue (WAT) stores fatty acids as triglycerides, and brown adipose tissue (BAT) oxidizes fatty acids to generate heat (thermogenesis). In the mitochondrial respiratory chain of brown adipose cells, the processes of electron transport and ATP production are uncoupled (dissociated) to permit the rapid production of heat from fatty acid oxidation (19).

Retinaldehyde dehydrogenase 1 (RALDH1), which converts retinal to retinoic acid, is highly expressed in WAT but not in BAT. The suppression of RALDH1 expression in WAT can induce a thermogenic phenotype resembling that of BAT (20). During adipocyte differentiation, the stimulation of cells with all-*trans* retinal has been found to activate the *UCP1* gene required for thermogenesis while inhibiting genes promoting adipogenesis, such as *PPARγ* (20). Retinal also appeared to regulate lipid metabolism and adiposity in bone marrow by inhibiting PPARγ/RXR heterodimer-mediated gene expression (21). In addition, retinal was found to inhibit gluconeogenic gene expression and glucose production in the liver of mice deficient in RALDH1 (22).

Immunity

Vitamin A was initially coined "the anti-infective vitamin" because of its importance in the normal functioning of the immune system (23). The skin and mucosal cells, lining the airways, digestive tract, and urinary tract function as a barrier and form the body's first line of defense against infection. Retinoic acid (RA) is produced by antigen-presenting cells (APCs), including macrophages and dendritic cells, found in these mucosal interfaces and associated lymph nodes. RA appears to act on dendritic cells themselves to regulate their differentiation, migration, and antigen-presenting capacity. In addition, the production of RA by APCs is required for the differentiation of naïve CD4 T-lymphocytes into induced regulatory T- lymphocytes (Tregs). Critical to the maintenance of mucosal integrity, the differentiation of Tregs is driven by all-*trans*-RA through RARα-mediated regulation of gene expression (see Regulation of gene expression). Also, during inflammation, all-*trans*-RA/RARα signaling pathway promotes the conversion of naïve CD4 T-lymphocytes into effector T-lymphocytes – type 1 helper T-cells (Th1) – (rather than into Tregs) and induces the production of proinflammatory cytokines by effector T-lymphocytes in response to infection. There is also substantial evidence to suggest that RA may help prevent the development of autoimmunity (reviewed in 24).

Prenatal and postnatal development

Both vitamin A excess and deficiency are known to cause birth defects. Retinoid signaling begins soon after the early phase of embryonic development known as gastrulation. During fetal development, RA is critical for the development of organs, including the heart, eyes, ears, lungs, as well as other limbs and visceral organs. Vitamin A has been implicated in fetal lung maturation (2). Vitamin A status is lower in preterm newborns than in full-term infants (25). There is some evidence to suggest that vitamin A supplementation may help reduce the incidence of chronic lung disease and mortality in preterm newborns (see Disease Prevention). Retinoid signaling is also involved in the expression of many proteins of the extracellular matrix (ECM; material surrounding cells), including collagen, laminin, and proteoglycans (26). Vitamin A deficiency may then result in alterations of the ECM composition, thus disrupting organ morphology and function (reviewed in 26).

Red blood cell production (erythropoiesis)

Red blood cells (erythrocytes), like all blood cells, are derived from pluripotent stem cells in the bone marrow. Studies involving *in vitro* culture systems have suggested a role for retinoids in stem cell commitment and differentiation to the red blood cell lineage. Retinoids might also regulate apoptosis (programmed cell death) of red blood cell precursors (erythropoietic progenitor cells) (27). However, whether retinoids regulate erythropoiesis *in vivo* has not been established. Yet, vitamin A supplementation in vitamin A deficient-individuals has been shown to increase hemoglobin concentrations. Additionally, vitamin A appears to facilitate the mobilization of iron from storage sites to the developing red blood cell for incorporation into hemoglobin, the oxygen carrier in red blood cells (27, 28).

Nutrient interactions

Zinc

Zinc deficiency is thought to interfere with vitamin A metabolism in several ways (29): (1) zinc deficiency results in decreased synthesis of retinol-binding protein (RBP), which transports retinol through the circulation to peripheral tissues and protects the organism against potential toxicity of retinol; (2) zinc deficiency results in decreased activity of the enzyme that releases retinol from its storage form, retinyl palmitate, in the liver; and (3) zinc is required for the enzyme that converts retinol into retinal (30). The health consequences of zinc deficiency on vitamin A nutritional status in humans are yet to be defined (29).

Iron

Vitamin A deficiency often coexists with iron deficiency and may exacerbate iron deficiency anemia by altering iron metabolism (27). Vitamin A supplementation has beneficial effects on iron deficiency anemia and improves iron nutritional status among children and pregnant women (27, 28). The combination of supplemental vitamin A and iron seems to reduce anemia more effectively than either supplemental iron or vitamin A alone (31). Moreover, studies in rats have shown that iron deficiency alters plasma and liver levels of vitamin A (32, 33).

Deficiency

Vitamin A deficiency usually results from inadequate intakes of vitamin A from animal products (as preformed vitamin A) and fruit and vegetables (as provitamin A carotenoids). In developing countries, vitamin A deficiency and associated disorders predominantly affect children and women of reproductive age. Other individuals at risk of vitamin A deficiency are those with poor absorption of lipids due to impaired pancreatic or biliary secretion and those with inflammatory bowel diseases, such as Crohn's disease and celiac disease (2). Subclinical vitamin A deficiency is often defined by serum retinol concentrations lower than 0.70 μmol/L (20 μg/dL). In severe vitamin A deficiency, vitamin A body stores are depleted and serum retinol concentrations fall below 0.35 μmol/L (10 μg/dL). Other biomarkers have been calibrated to assess vitamin A nutritional status (reviewed in 34). Of note, the World Health Organization considers vitamin A deficiency a public health problem when the prevalence of low serum retinol (<0.70 μmol/L) reaches 15% or more of a defined population.

Vitamin A deficiency-related disorders

Disease of the eye and blindness

With an estimated 250,000 to 500,000 children becoming blind annually, vitamin A deficiency constitutes the leading preventable cause of blindness in low- and middle-income nations (35). The earliest symptom of vitamin A deficiency is impaired dark adaptation known as night blindness or nyctalopia. The next clinical stage is the occurrence of abnormal changes in the conjunctiva (corner of the eye), manifested by the presence of Bitot's spots. Severe or prolonged vitamin A deficiency eventually results in a condition called xerophthalmia (Greek for dry eye), characterized by changes in the cells of the cornea (clear covering of the eye) that ultimately result in corneal ulcers, scarring, and blindness (36). Immediate administration of 200,000 international units (IU) of vitamin A for two consecutive days is required to prevent blinding xerophthalmia (36).

There is an estimated 19.1 million pregnant women worldwide (especially in Sub-Saharan Africa, Southeast Asia, and Central America) with vitamin A deficiency and over half of them are affected by night blindness (37). The prevalence of vitamin A deficiency and night blindness is especially high during the third trimester of pregnancy due to accelerated fetal growth. Also, approximately 190 million preschool-age children have low serum retinol concentrations (<0.70 μmol/L), with 5.2 million suffering from night blindness. Moreover, half of the children affected by severe vitamin A deficiency-induced blinding xerophthalmia are estimated to die within a year of becoming blind (37). The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) promote vitamin A supplementation as a public health intervention to reduce child mortality in areas and populations where vitamin A deficiency is prevalent (38-40).

Susceptibility to infectious diseases

Infectious diseases have been associated with depletion of vitamin A hepatic reserves (already limited in vitamin A-deficient subjects), reduced serum retinol concentrations, and increased loss of vitamin A in the urine (37). Infection with the measles virus was found to precipitate conjunctival and corneal damage, leading to blindness in children with poor vitamin A status (41). Conversely, vitamin A deficiency can be considered a nutritionally acquired immunodeficiency disease (42). Even children who are only mildly deficient in vitamin A have a higher incidence of respiratory complications and diarrhea, as well as a higher rate of mortality from measles infection compared to children consuming sufficient vitamin A (43). Because vitamin A supplementation may decrease both the severity and incidence of measles complications in developing countries (see Disease Prevention), WHO recommends that children aged at least one year receive 200,000 IU of vitamin A (60 mg RAE) for two consecutive days in addition to standard treatment when they are infected with measles virus and live in areas of vitamin A deficiency (44).

A recent prospective cohort study, conducted in 2,774 Colombian children (ages, 5-12 years old) followed for a median 128 days, also reported an inverse relationship between plasma retinol concentrations and rates of diarrhea with vomiting and cough with fever, the latter being a strong predictor of influenza infection (flu) (45). A review of five randomized, placebo-controlled studies that included 7,528 HIV-positive pregnant or breast-feeding women found no substantial benefit of vitamin A supplementation in reducing the mother-to-child transmission of HIV (46). One early observational study found that HIV-infected women who were vitamin A deficient were three to four times more likely to transmit HIV to their infants (47). Yet, no trial to date has provided any information on potential adverse effects of vitamin A supplementation on mother-to-child HIV transmission (48).

Thyroid dysfunction

In North and West Africa, vitamin A deficiency and iodine deficiency induced-goiter can coexist in up to 50% of children. The response to iodine prophylaxis in iodine-deficient populations appears to depend on various nutritional factors, including vitamin A status (49, 50). Vitamin A deficiency in animal models was found to interfere with the pituitary-thyroid axis by (1) increasing the synthesis and secretion of thyroid-stimulating hormone (TSH) by the pituitary gland, (2) increasing the size of the thyroid gland, (3) reducing iodine uptake by the thyroid gland and impairing the synthesis and iodination of thyroglobulin, and (4) increasing circulating concentrations of thyroid hormones (reviewed in 51). A cross-sectional study of 138 children with concurrent vitamin A and iodine deficiencies found that the severity of vitamin A deficiency was associated with higher risk of goiter and higher concentrations of circulating TSH and thyroid hormones (50). These children received iodine-enriched salt with either vitamin A (200,000 IU at baseline and 5 months) or placebo in a randomized, double-blind, 10-month trial. This vitamin A supplementation significantly decreased TSH concentration and thyroid volume compared to placebo (50). In another trial, supplementation of vitamin A to iodine-deficient children had no additional effect to iodine on thyroid status compared to placebo, but vitamin A supplementation alone (without iodine) reduced the volume of the thyroid gland, as well as TSH and thyroglobulin concentrations (52).

Other disorders

Phrynoderma or follicular hyperkeratosis is a skin condition characterized by an excessive production of keratin in hair follicles. The lesions first appear on the extremities, shoulders, and buttocks and may spread over the entire body in the severest cases (53). While vitamin A deficiency may contribute to the occurrence of phrynoderma, the condition has been strongly associated with multiple nutritional deficiencies and is considered a sign of general malnutrition. A rare case of esophagitis (inflammation of the esophagus) has recently been attributed to hyperkeratosis secondary to vitamin A deficiency (54).

Also, vitamin A deficiency affects iron mobilization, impairs hemoglobin synthesis, and precipitates iron deficiency anemia that is only alleviated with supplementation of both vitamin A and iron (see Nutrient interactions) (27).

The Recommended Dietary Allowance (RDA)

Retinol Activity Equivalents (RAE)

Vitamin A can be obtained from food as preformed vitamin A in animal products or as provitamin A carotenoids in fruit and vegetables (see Food sources). Yet, while preformed vitamin A is effectively absorbed, stored, and hydrolyzed to form retinol, provitamin A carotenoids like β-carotene are less easily digested and absorbed, and must be converted to retinol and other retinoids by the body after uptake into the small intestine. The efficiency of conversion of provitamin A carotenes into retinol is highly variable, depending on factors such as food matrix, food preparation, and one's digestive and absorptive capacities (55).

The most recent international standard of measure for vitamin A is retinol activity equivalents (RAE), which represent vitamin A activity as retinol. It has been determined that 2 micrograms (μg) of β-carotene in oil provided as a supplement could be converted by the body to 1 μg of retinol giving it an RAE ratio of 2:1. However, 12 μg of β-carotene from food are required to provide the body with 1 μg of retinol, giving dietary β-carotene an RAE ratio of 12:1. Other provitamin A carotenoids in food are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1. RAE ratios are shown in **Table 1** (56).

Table 1. Retinol activity equivalents (RAE) Ratios for Preformed Vitamin A and Provitamin A Carotenoids

Quantity Consumed	Quantity Bioconverted to Retinol	RAE Ratio
1 μg of dietary or supplemental vitamin A	1 μg of retinol*	1:1
2 μg of supplemental β-carotene	1 μg of retinol	2:1
12 μg of dietary β-carotene	1 μg of retinol	12:1
24 μg of dietary α-carotene	1 μg of retinol	24:1
24 μg of dietary β-cryptoxanthin	1 μg of retinol	24:1

*1 IU is equivalent to 0.3 microgram (μg) of retinol, and 1 μg of retinol is equivalent to 3.33 IU of retinol.

Determination of the RDA

The RDA for vitamin A was revised by the Food and Nutrition Board (FNB) of the US Institute of Medicine (IOM) in 2001. The RDA is based on the Estimated Average Requirement (EAR), which is defined as the biological requirement for 50% of the population. The RDA is the recommended intake needed by nearly all of the population to ensure adequate hepatic stores of vitamin A in the body (20 μg/g for four months if the person consumes a vitamin A-deficient diet) to support normal reproductive function, immune function, gene expression, and vision (for details of calculations, see 56). **Table 2** lists the RDA values in micrograms (μg) of Retinol Activity Equivalents (RAE) per day.

Table 2. Recommended Dietary Allowance (RDA) for Vitamin A as Preformed Vitamin A (micrograms [μg] of Retinol Activity Equivalents [RAE]/day)

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	400 (AI)	400 (AI)
Infants	7-12 months	500 (AI)	500 (AI)
Children	1-3 years	300	300
Children	4-8 years	400	400
Children	9-13 years	600	600
Adolescents	14-18 years	900	700
Adults	19 years and older	900	700
Pregnancy	18 years and younger	-	750
Pregnancy	19 years and older	-	770
Breast-feeding	18 years and younger	-	1,200
Breast-feeding	19 years and older	-	1,300

Disease Prevention

Bronchopulmonary dysplasia in preterm infants

Preterm infants are born with inadequate body stores of vitamin A, placing them at risk of developing diseases of the eye and the respiratory and gastrointestinal tracts. About one-third of preterm infants born between 22 and 28 weeks of gestation develop bronchopulmonary dysplasia (BPD), a chronic lung disease that can be fatal or result in life-long morbidities in survivors. A few randomized controlled studies have investigated the effect of postnatal vitamin A supplementation on the incidence of BPD and the risk of mortality in very low birth weight infants (≤1,500 g) requiring respiratory support (57-59). In the largest, multicenter, randomized, blinded, placebo-controlled trial that enrolled 807 extremely low birth weight (ELBW; ≤1,000 g) preterm newborns, the intramuscular administration of 5,000 IU of vitamin A three times a week for four weeks significantly, though modestly, reduced the risk of BPD or death at 36 weeks' postmenstrual age (gestational age plus chronological age) (58). While vitamin A supplementation was included in some neonatal programs after this trial (60), a national shortage in vitamin A supply that has affected US neonatal intensive care units since 2010 has led to a significant reduction in the use of vitamin A supplementation in premature newborns (401-1,000 g at birth) with respiratory failure (61, 62). However, a retrospective analysis of US nationwide data from 6,210 preterm infants born between 2010 and 2012 found that a reduction in vitamin A prophylaxis from 27.2% to 2.1% during the same period had no significant impact on the incidence of BPD or death before hospital discharge (62).

In another retrospective study, the nonrandomized use of vitamin A supplementation with inhaled nitric oxide (iNO) was found to result in a lower incidence of BPD (but not mortality) compared to iNO therapy alone in preterm newborns with a birth weight of 750-999 g (63). Neurodevelopment index scores at one year of age were also improved in the vitamin A group of newborns weighing 500-749 g at birth. Yet, caution is advised with the interpretation of the results, especially because the trial was not designed to assess the effect of vitamin A. In Germany, one large, multicenter, randomized study – the NeoVitaA trial – is under way to explore the effect of high-dose oral vitamin A (5,000 IU/kg/day) for 28 days on the incidence of BPD and mortality at 36 weeks' postmenstrual age (64).

While high doses of vitamin A during early pregnancy can cause birth defects (see Safety), vitamin A supplementation during late pregnancy may improve maternal and fetal vitamin A status (65). Although a few randomized controlled trials have failed to show an effect on maternal and neonatal mortality (66), more research is required to assess whether vitamin A supplementation during pregnancy reduces BPD incidence in infants.

Childhood morbidity and mortality

A recent meta-analysis of randomized controlled trials evaluating the preventive effect of vitamin A on childhood mortality indicated that vitamin A supplementation (200,000 IU every 4 or 6 months) reduced all-cause mortality by 25% (13 studies) and diarrhea-specific mortality by 30% (7 studies) in children aged 6 to 59 months. However, vitamin A administration in this age group had no preventive effect on rates of pneumonia-specific mortality (7 studies), measles-specific mortality (5 studies), or meningitis-specific mortality (3 studies). Moreover, no reduction in the risk of disease-specific mortality was found in neonates (0 to 28 days of age) and infants 1 to 6 months of age supplemented with vitamin A (67). Another meta-analysis of randomized controlled trials found no evidence of a reduction in mortality risk during infancy when either breast-feeding mothers (7 studies) or infants aged less than six months (9 studies) were supplemented with vitamin A (68).

Current WHO policy recommends vitamin A supplementation at routine vaccination contacts in children after six months of age living in regions at high risk of vitamin A deficiency. Supplementation with high doses of vitamin A – 100,000 IU (30 mg RAE) for infants 6 to 11 months of age and 200,000 IU (60 mg RAE) for children 12 to 59 months of age – is thought to provide adequate protection for up to six months (38). A recent placebo-controlled trial in Guinea-Bissau, which randomized 7,587 children (ages, 6 to 23 months old) to receive vitamin A supplementation at one vaccination contact, evaluated the co-administration of vitamin A and vaccines on child mortality (69). The study found that vitamin A supplementation had no effect on overall mortality rates, although a six-month follow-up of infants given both measles and DTP (diphtheria-tetanus-pertussis) vaccinations showed a significant reduction in mortality in girls, but not in boys (69). Although neonatal vitamin A supplementation is not currently recommended, a trial assessing the benefit of early measles vaccination – at 4.5 rather than the usual 9 months of age – found no reduction in mortality rates when children had received neonatal vitamin A supplementation (70). The recent pooled analysis of previous trials of vitamin A supplementation (VITA I-III) in Guinea-Bissau confirmed that vitamin A supplementation may interfere with vaccines. Specifically, compared to placebo, neonatal vitamin A supplementation was associated with a significant increase in mortality rates in boys (but not in girls) when children had received measles virus vaccination at 4.5 months of age rather than the usual 9 months of age (71). The timing of vitamin A interventions needs to be further examined in relation to the timing of vaccinations in order to maximize their benefits.

Complications from measles infection

An earlier meta-analysis of seven randomized controlled trials examining specifically the role of vitamin A supplementation in 2,069 children with measles found no overall reduction on the risk of mortality (72). Yet, the pooled analysis of four studies that reported the age distribution of participants found an 83% lower risk of mortality with two doses of 200,000 IU of vitamin A in children younger than two years. In addition, the pooled analysis of three studies indicated a 67% reduction in the risk of pneumonia-led mortality (72). Similar to WHO and UNICEF guidelines, the American Academy of Pediatrics recommends vitamin A supplementation for children over six months of age when they are infected with measles while malnourished, immunodeficient, or are at risk of measles complications or vitamin A deficiency disorders (73). Although measles infection has been associated with vitamin A deficiency and blindness, there is currently no evidence to suggest that vitamin A supplementation reduces the risk of blindness in children infected with measles (74).

Cancer

Studies in cell culture and animal models have documented the capacity for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, prostate, and other sites. However, the results of human studies examining the relationship between the consumption of preformed vitamin A and cancer do not currently suggest that consuming vitamin A at intakes greater than the RDA benefit in the prevention of cancer (2).

Lung cancer

The results of the β-Carotene And Retinol Efficacy Trial (CARET) have suggested that high-dose supplementation of preformed vitamin A and β-carotene should be avoided in people at high risk for lung cancer (75). In the CARET study, about 9,000 people (smokers and people with asbestos exposure) were assigned a daily regimen of 25,000 IU (7,500 μg RAE) of retinyl palmitate and 30 mg of β-carotene, while a similar number of people were assigned a placebo. After four years of follow-up, the incidence of lung cancer was 28% higher in the supplemented group compared to the placebo group; however, the incidence was not different six years after the intervention ended (76). A possible explanation for an increase in lung cancer is that the oxidative environment of the lung, created by smoke or asbestos exposure, could give rise to unusual carotenoid cleavage products, which might promote carcinogenesis (77). Interestingly, a case-control study that included 749 lung cancer cases and 679 controls from the CARET trial found a significant association between lung cancer risk reduction and high vitamin D intakes (≥400 IU/day) in individuals who received the active CARET supplements or in those with vitamin A intakes equal to or greater than 1,500 μg RAE/day (78). Further, a recent meta-analysis of four randomized controlled trials, including a total of 202,924 participants at low risk of lung cancer, indicated that supplementation with retinol and/or β-carotene had no significant effect on lung cancer incidence (79). At present, it seems unlikely that increased intake of preformed vitamin A (e.g., retinol) could lower the risk of lung cancer.

Disease Treatment

Retinoids may be used at pharmacological doses to treat several conditions, including, acute promyelocytic leukemia, retinitis pigmentosa, and various skin diseases. It is important to note that treatment with high doses of natural or synthetic retinoids overrides the body's own control mechanisms; therefore, retinoid therapies are associated with potential side effects and toxicities. Additionally, all of the retinoid compounds have been found to cause fetal deformations. Thus, women who have a chance of becoming pregnant should avoid treatment with these medications. Retinoids tend to be very long acting: side effects and birth defects have been reported to occur months after discontinuing retinoid therapy (2). The retinoids discussed below are prescription drugs and should not be used without medical supervision.

Acute promyelocytic leukemia

Normal differentiation of myeloid stem cells in the bone marrow gives rise to platelets, red blood cells, and white blood cells (also called leukocytes) that are important for the immune response. Altered differentiation of myeloid cells can result in the proliferation of immature white blood cells, giving rise to leukemia. Reciprocal chromosome translocations involving the promyelocytic leukemia (PML) gene and the gene coding for retinoic acid receptor α (RARα) lead to a specific type of leukemia called acute promyelocytic leukemia (APL). The fusion protein PML/RARα represses transcription by binding to RARE in the promoter of retinoid-responsive genes involved in hematopoietic cell differentiation. Gene repression by PML/RARα is achieved by the recruitment of several chromatin modifiers, including histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). Contrary to RARα wild-type receptor, PML/RARα appears to be insensitive to physiological concentrations of retinoic acid (RA) such that only treatments with high doses of all-*trans*-RA can restore normal differentiation and lead to significant improvements and complete remission in some APL patients (80).

More information on APL treatment programs can be found in the National Cancer Institute website.

Diseases of the skin

Both natural and synthetic retinoids have been used as pharmacologic agents to treat disorders of the skin. Acitretin is a synthetic retinoid that has been proven useful in combination treatments for psoriasis (81). Topical tretinoin (all-*trans*-retinoic acid) and oral isotretinoin (13-*cis*-retinoic acid) have been used successfully to treat mild-to-severe acne vulgaris (82, 83). Retinoids exhibit anti-inflammatory properties and regulate the proliferation and differentiation of skin epithelial cells, as well as the production of sebum. Use of pharmacological doses of retinoids (especially oral isotretinoin) by pregnant women causes birth defects and is therefore contraindicated prior to and during pregnancy (see Safety in pregnancy).

For more information on the use of retinoids in the management of acne, see the article on Vitamin A and Skin Health.

Retinitis pigmentosa

Retinitis pigmentosa (RP) affects approximately 1.5 million people worldwide and is a leading cause of inherited blindness. RP describes a broad spectrum of genetic disorders that result in the progressive loss of photoreceptor cells (rods and cones) in the retina of the eye (84). While at least 45 loci have been associated with RP, mutations in the rhodopsin gene (*RHO*), the usherin gene (*USH2A*), and the RP GTPase regulator gene (*RPGR*) account for about 30% of all RP cases (85).

Early symptoms of RP include impaired dark adaptation and night blindness, followed by the progressive loss of peripheral and central vision over time (85). The results of only one randomized controlled trial in 601 patients with common forms of RP indicated that supplementation with 15,000 IU/day of retinyl palmitate (4,500 μg RAE) significantly slowed the loss of retinal function over a period of four to six years (86). In contrast, supplementation with 400 IU/day of vitamin E (*dl*-α-tocopherol) modestly but significantly increased the loss of retinal function, suggesting that patients with common forms of RP may benefit from long-term vitamin A supplementation but should avoid high-dose vitamin E supplementation. Up to 12 years of follow-up in these patients did not reveal any signs of liver toxicity as a result of excess vitamin A intake (87). Because neither children younger than 18 years nor adults affected by less common forms of RP were included in the trial, no formal recommendation about vitamins A and E could be made (85). High-dose vitamin A supplementation to slow the course of RP requires medical supervision and must be discontinued if there is a possibility of pregnancy (see Safety).

Sources

Food sources

Free retinol is not generally found in food. Retinyl esters (including retinyl palmitate) are the storage form of retinol in animals and thus the main precursors of retinol in food from animals. Plants contain carotenoids, some of which are precursors for vitamin A (e.g., α-carotene, β-carotene, and β-cryptoxanthin). Yellow- and orange-colored vegetables contain significant quantities of carotenoids. Green vegetables also contain carotenoids, though yellow-to-red pigments are masked by the green pigment of chlorophyll (1). The table below lists a number of good food sources of vitamin A, including fruit and vegetables, along with their vitamin A content. The retinol activity is indicated in micrograms of retinol activity equivalents (μg RAE). For information on this unit of measurement, see the section on RAE. In addition, use USDA's FoodData Central to check foods for their content of carotenoids without vitamin A activity, such as lycopene, lutein, and zeaxanthin.

Vitamin A international units (IUs)

Vitamin A may still be listed on food and supplement labels in international units versus as μg RAE ('mcg' on labels). USDA's FoodData Central also provides the vitamin A content of food sources using the vitamin A international unit (IU). Yet, contrary to RAE, the number of IUs of vitamin A does not reflect the bioavailability of vitamin A from different food sources. Conversion rates between IUs and μg RAE are set as follows:

- 1 IU of retinol is equivalent to 0.3 μg RAE
- 1 IU of supplemental β-carotene is equivalent to 0.3 μg RAE
- 1 IU of dietary β-carotene is equivalent to 0.05 μg RAE
- 1 IU of α-carotene or β-cryptoxanthin to 0.025 μg RAE

Thus, in **Table 3**, the number of IUs of vitamin A in carotenoid-containing food (numbers in italics) can be obtained by multiplying the RAE by approximately 20.

Table 3. Some Food Sources of Vitamin A

Food	Serving	Preformed Vitamin A (Retinol), μg	Vitamin A, μg RAE	Vitamin A, IU
Beef liver, cooked	1 slice (68 g)	6,421*	6,421*	21,566*
Cod liver oil	1 teaspoon	1,350	1,350	4,500
Fortified breakfast cereal (oats)	1 serving (1 oz)	216	216	721
Egg	1 large	80	80	270
Butter	1 tablespoon	95	95	355
Whole milk	1 cup (8 fl oz)	110	110	395
2% fat milk (vitamin A added)	1 cup (8 fl oz)	134	134	464
Nonfat milk (vitamin A added)	1 cup (8 fl oz)	149	149	500
Sweet potato (canned, mashed)	½ cup	0	555	*11,091*
Sweet potato (baked)	½ cup	0	961	*19,218*
Pumpkin (canned)	½ cup	0	953	*19,065*
Carrot (raw, chopped)	½ cup	0	534	*10,692*
Cantaloupe	½ medium melon	0	466	*9,334*
Mango	1 fruit	0	181	*3,636*
Spinach (cooked)	½ cup	0	472	*9,433*
Broccoli (cooked)	½ cup	0	60	*1,207*
Kale (cooked)	½ cup	0	443	*8,854*
Collards (cooked)	½ cup	0	361	*7,220*
Squash, butternut (cooked)	½ cup	0	572	*11,434*

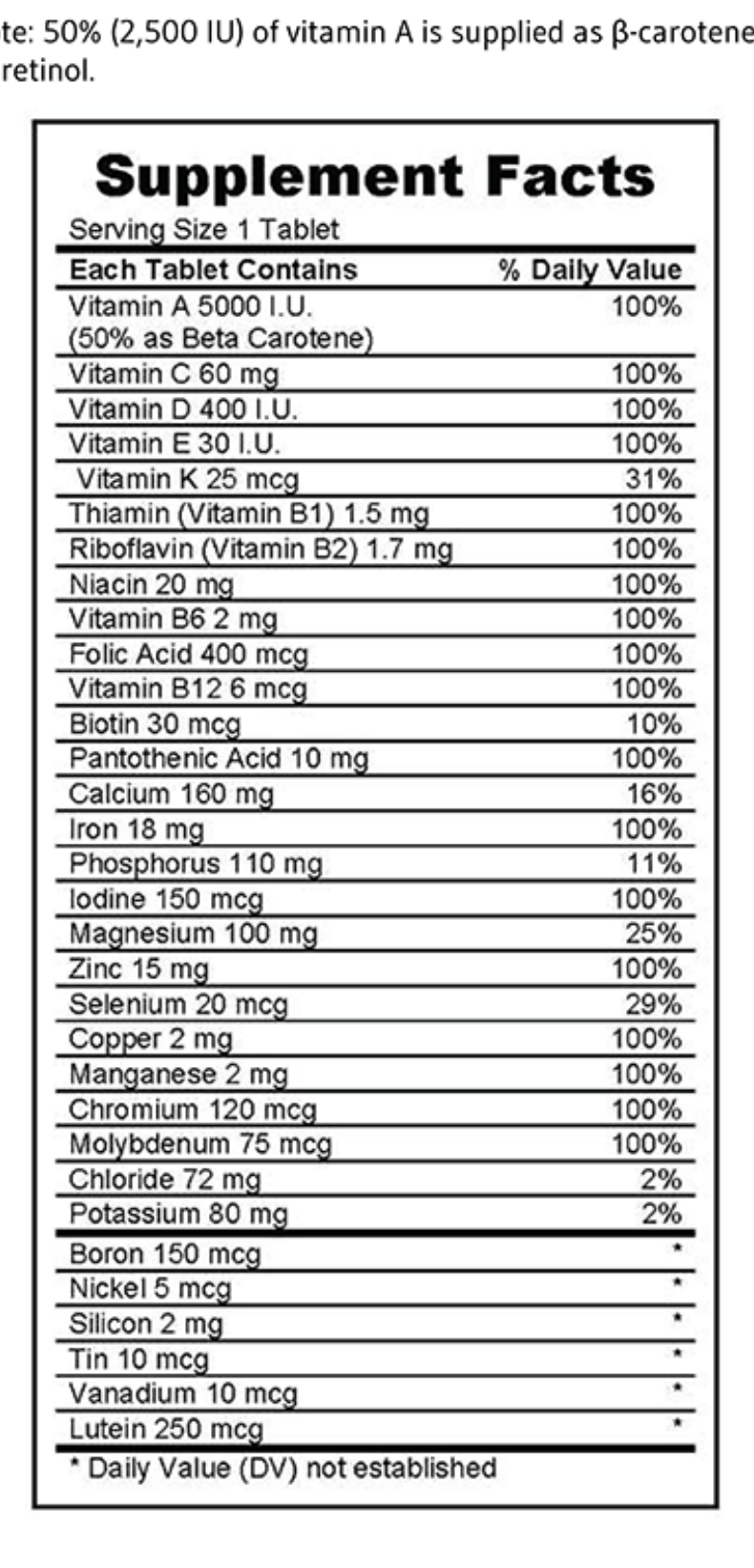
*Above the tolerable upper intake level (UL) of 3,000 μg RAE (10,000 IU)/day

Supplements

The principal forms of preformed vitamin A in supplements are retinyl palmitate and retinyl acetate. β-Carotene is also a common source of vitamin A in supplements, and many supplements provide a combination of retinol and β-carotene (88). If a percentage of the total vitamin A content of a supplement comes from β-carotene, this information is included in the Supplement Facts label under vitamin A (**Figure 4**). Some multivitamin supplements available in the US provide up to 5,000 IU of preformed vitamin A, corresponding to 1,500 μg RAE, which is substantially more than the current RDA for vitamin A. This is due to the fact that the Daily Values (DV) used by the US Food and Drug Administration (FDA) for supplement labeling are based on the RDA established in 1968 rather than the most recent RDA, and multivitamin supplements typically provide 100% of the DV for most nutrients. Because retinol intakes of 5,000 IU/day (1,500 μg RAE) may be associated with an increased risk of osteoporosis in older adults (see Safety), some companies have reduced the retinol content in their multivitamin supplements to 2,500 IU (750 μg RAE).

Figure 4. An Example of a Multivitamin/Mineral Supplement Label

Note: 50% (2,500 IU) of vitamin A is supplied as β-carotene, while the rest (2,500 IU) is supplied as retinol.



Supplement Facts

Serving Size 1 Tablet

Each Tablet Contains	% Daily Value
Vitamin A 5000 I.U. (50% as Beta Carotene)	100%
Vitamin C 60 mg	100%
Vitamin D 400 I.U.	100%
Vitamin E 30 I.U.	100%
Vitamin K 25 mcg	31%
Thiamin (Vitamin B1) 1.5 mg	100%
Riboflavin (Vitamin B2) 1.7 mg	100%
Niacin 20 mg	100%
Vitamin B6 2 mg	100%
Folic Acid 400 mcg	100%
Vitamin B12 6 mcg	100%
Biotin 30 mcg	10%
Pantothenic Acid 10 mg	100%
Calcium 160 mg	16%
Iron 18 mg	100%
Phosphorus 110 mg	11%
Iodine 150 mcg	100%
Magnesium 100 mg	25%
Zinc 15 mg	100%
Selenium 20 mcg	29%
Copper 2 mg	100%
Manganese 2 mg	100%
Chromium 120 mcg	100%
Molybdenum 75 mcg	100%
Chloride 72 mg	2%
Potassium 80 mg	2%
Boron 150 mcg	*
Nickel 5 mcg	*
Silicon 2 mg	*
Tin 10 mcg	*
Vanadium 10 mcg	*
Lutein 250 mcg	*

* Daily Value (DV) not established

Safety

Toxicity

The condition caused by vitamin A toxicity is called hypervitaminosis A. It is caused by overconsumption of preformed vitamin A, not carotenoids. Preformed vitamin A is rapidly absorbed and slowly cleared from the body. Therefore, toxicity from preformed vitamin A may result acutely from high-dose exposure over a short period of time or chronically from a much lower intake (2). Acute vitamin A toxicity is relatively rare, and symptoms include nausea, headache, fatigue, loss of appetite, dizziness, dry skin, desquamation, and cerebral edema. Signs of chronic toxicity include dry itchy skin, desquamation, anorexia, weight loss, headache, cerebral edema, enlarged liver, enlarged spleen, anemia, and bone and joint pain. Also, symptoms of vitamin A toxicity in infants include bulging fontanels. Severe cases of hypervitaminosis A may result in liver damage, hemorrhage, and coma. Generally, signs of toxicity are associated with long-term consumption of vitamin A in excess of 10 times the RDA (8,000-10,000 μg RAE/day or 25,000-33,000 IU/day). However, more research is necessary to determine if subclinical vitamin A toxicity is a concern in certain populations (89). There is evidence that some populations may be more susceptible to toxicity at lower doses, including the elderly, chronic alcohol users, and some people with a genetic predisposition to high cholesterol (90). In January 2001, the Food and Nutrition Board of the US Institute of Medicine set the tolerable upper intake level (UL) of vitamin A intake for adults at 3,000 μg RAE (10,000 IU)/day of preformed vitamin A (56).

Table 4. Tolerable Upper Intake Level (UL) for Preformed Vitamin A

Age Group	μg RAE/day	IU/day*
Infants 0-12 months	600	2,000
Children 1-3 years	600	2,000
Children 4-8 years	900	3,000
Children 9-13 years	1,700	5,667
Adolescents 14-18 years	2,800	9,333
Adults 19 years and older	3,000	10,000

*1 IU of preformed vitamin A is equivalent to 0.3 μg RAE, and 1 μg RAE is equivalent to 3.33 IU of preformed vitamin A

Safety in pregnancy

Although normal fetal development requires sufficient vitamin A intake, consumption of excess preformed vitamin A (such as retinol) during early pregnancy is known to cause birth defects. No increase in the risk of vitamin A-associated birth defects has been observed at doses of preformed vitamin A from supplements below 3,000 μg RAE/day (10,000 IU/day) (56). Of note, in 2011, the World Health Organization (WHO) recommended vitamin A supplementation (up to 3,000 μg RAE/day or 7,500 μg RAE/week) during pregnancy in areas with high prevalence of vitamin A deficiency for the prevention of blindness (91). In industrialized countries, pregnant or potentially pregnant women should monitor their intake of vitamin A from fortified food and food naturally high in preformed vitamin A (e.g., liver) and avoid taking daily multivitamin supplements that contain more than 1,500 μg RAE (5,000 IU) of vitamin A. There is no evidence that consumption of vitamin A from β-carotene might increase the risk of birth defects. The synthetic derivative of retinol, isotretinoin, is known to cause serious birth defects and should not be taken during pregnancy or if there is a possibility of becoming pregnant (82). Tretinoin (all-*trans*-retinoic acid), another retinol derivative, is prescribed as a topical preparation that is applied to the skin. Although percutaneous absorption of topical tretinoin is minimal, its use during pregnancy is not recommended (92).

Do high intakes of vitamin A increase the risk of osteoporosis?

Results from some prospective studies have suggested that long-term intakes of preformed vitamin A in excess of 1,500 μg RAE/day (equivalent to 5,000 IU/day of vitamin A as retinol) were associated with reduced bone mineral density (BMD) and increased risk of osteoporotic fracture in older adults (93-95). However, other investigators failed to observe such detrimental effects on BMD and/or fracture risk (96-98). The recent meta-analysis of four prospective studies, including nearly 183,000 participants over 40 years of age, found that highest vs. lowest quintiles of retinol (preformed vitamin A) intake significantly increased the risk of hip fracture (99). Only excess intakes of retinol, not β-carotene, were associated with adverse effects on bone health. Besides, the pooled analysis of four observational studies also indicated that a U-shaped relationship between circulating retinol and risk of hip fracture, suggesting that both elevated and reduced retinol concentrations in the blood were associated with an increased risk of hip fracture (99).

To date, limited experimental data have suggested that vitamin A (as all-*trans*-retinoic acid) may affect the development of bone-remodeling cells and stimulate bone matrix degradation (resorption) (reviewed in 100). Vitamin A may also interfere with the ability of vitamin D to maintain calcium balance (101). In the large Women's Health Initiative (WHI) prospective study, the highest vs. lowest quintile of retinol intake (≥1,426 μg/day vs. <474 μg/day) was found to be significantly associated with increased risk of fracture only in women with the lowest vitamin D intakes (≤440 IU/day) (102).

Until supplements and fortified food are reformulated to reflect the current RDA for vitamin A, it is advisable for older individuals to consume multivitamin supplements that contain no more than 2,500 IU (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene.

Drug interactions

Chronic alcohol consumption results in depletion of liver stores of vitamin A and may contribute to alcohol-induced liver damage (cirrhosis) (103). However, the liver toxicity of preformed vitamin A (retinol) is enhanced by chronic alcohol consumption, thus narrowing the therapeutic window for vitamin A supplementation in alcoholics (103). Oral contraceptives that contain estrogen and progestin increase retinol binding protein (RBP) synthesis by the liver, increasing the export of all-*trans*-retinol/RBP complex to the circulation. Whether this increases the dietary requirement of vitamin A is not known. Also, the use of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, mineral oil, and the fat substitute, olestra, which interfere with fat absorption, may affect the absorption of fat-soluble vitamins, including vitamin A (88). Further, intake of large doses of vitamin A may decrease the absorption of vitamin K. Retinoids or retinoid analogs, including acitretin, all-*trans*-retinoic acid, bexarotene, etretinate, and isotretinoin, should not be used in combination with single-nutrient vitamin A supplements, because they may increase the risk of vitamin A toxicity (88).

Linus Pauling Institute Recommendation

The RDA for vitamin A (700 μg RAE/day for women and 900 μg RAE/day for men) is sufficient to support normal gene expression, immune function, and vision. However, following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement daily could supply as much as 5,000 IU (1,500 μg RAE)/day of vitamin A as retinol, the amount that has been associated with adverse effects on bone health in older adults. For this reason, we recommend taking a multivitamin/mineral supplement that provides no more than 2,500 IU (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene. High potency vitamin A supplements should not be used without medical supervision due to the risk of toxicity.

Older adults (>50 years)

Presently, there is little evidence that the requirement for vitamin A in older adults differs from that of younger adults. Additionally, vitamin A toxicity may occur at lower doses in older adults than in younger adults. Further, data from observational studies suggested an association between intakes of preformed vitamin A in excess of 1,500 μg RAE (5,000 IU)/day and increased risk of hip fracture in older people (see Safety). Yet, following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement daily could supply as much as 5,000 IU/day of retinol, the amount that has been associated with adverse effects on bone health in older adults. For this reason, we recommend taking a multivitamin/mineral supplement that provides (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene. As for all age groups, high potency vitamin A supplements should not be used without medical supervision due to the risk of toxicity.

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Vitamin B6

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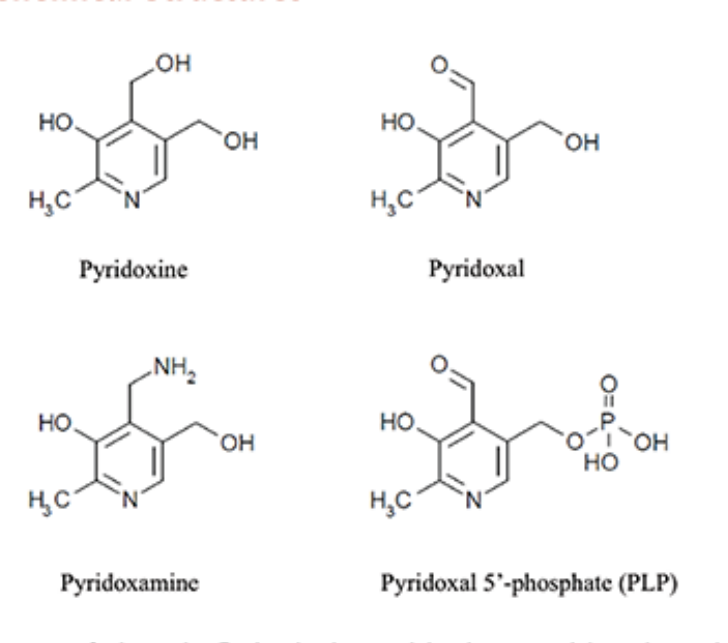
Summary

- Vitamin B_6 and its derivative pyridoxal 5'-phosphate (PLP) are essential to over 100 enzymes mostly involved in protein metabolism. *(More information)*
- High levels of circulating homocysteine are associated with an increased risk of cardiovascular disease. Randomized controlled trials have demonstrated that supplementation with B vitamins, including vitamin B_6, could effectively reduce homocysteine levels. However, homocysteine lowering by B vitamins has failed to lower the risk of adverse cardiovascular outcomes in high-risk individuals. *(More information)*
- Growing evidence from experimental and clinical studies suggests that systemic inflammation underlying most chronic diseases may impair vitamin B_6 metabolism. *(More information)*
- Although supplementation with vitamin B_6 and other B vitamins has not been associated with improved cognitive performance or delayed cognitive deterioration in the elderly, recent studies suggest that vitamin B_6 might help reduce the risk of late-life depression. *(More information)*
- Pharmacologic doses of vitamin B_6 are used to treat seizures in rare inborn errors of vitamin B_6 metabolism. Also, randomized controlled trials support the use of vitamin B_6 to treat morning sickness in pregnant women and suggest a possible benefit in the management of premenstrual syndrome and carpal tunnel syndrome. *(More information)*
- Vitamin B_6 is found in a variety of foods, including fish, poultry, nuts, legumes, potatoes, and bananas. *(More information)*
- Several medications, including anti-tuberculosis drugs, anti-parkinsonians, nonsteroidal anti-inflammatory drugs, and oral contraceptives, may interfere with vitamin B_6 metabolism. *(More information)*

Vitamin B_6 is a water-soluble vitamin that was first isolated in the 1930s. The term vitamin B_6 refers to six common forms, namely pyridoxal, pyridoxine (pyridoxol), pyridoxamine, and their phosphorylated forms. The phosphate ester derivative pyridoxal 5'-phosphate (PLP) is the bioactive coenzyme form involved in over 4% of all enzymatic reactions (**Figure 1**) (1-3).

Figure 1. Vitamin B_6 Chemical Structures



Non-phosphorylated forms of vitamin B_6 include pyridoxine, pyridoxal, and pyridoxamine. While all three of these variants can be phosphorylated, the phosphate ester derivative of pyridoxal, pyridoxal 5'-phosphate (PLP), is the cofactor of most vitamin B_6-dependent enzymes in the body.

Function

Vitamin B_6 must be obtained from the diet because humans cannot synthesize it. PLP plays a vital role in the function of over 100 enzymes that catalyze essential chemical reactions in the human body (4). PLP-dependent enzymes have been classified into five structural classes known as Fold Type I-V (5):

- Fold Type I - aspartate aminotransferase family
- Fold Type II - tryptophan synthase family
- Fold Type III - alanine racemase family
- Fold Type IV - D-amino acid aminotransferase family
- Fold Type V - glycogen phosphorylase family

The many biochemical reactions catalyzed by PLP-dependent enzymes are involved in essential biological processes, such as hemoglobin and amino acid biosynthesis, as well as fatty acid metabolism. Of note, PLP also functions as a coenzyme for glycogen phosphorylase, an enzyme that catalyzes the release of glucose from stored glycogen. Much of the PLP in the human body is found in muscle bound to glycogen phosphorylase. PLP is also a coenzyme for reactions that generate glucose from amino acids, a process known as gluconeogenesis (6).

Nervous system function

In the brain, the PLP-dependent enzyme aromatic L-amino acid decarboxylase catalyzes the synthesis of two major neurotransmitters: serotonin from the amino acid tryptophan and dopamine from L-3,4-dihydroxyphenylalanine (L-Dopa). Other neurotransmitters, including glycine, D-serine, glutamate, histamine, and γ-aminobutyric acid (GABA), are also synthesized in reactions catalyzed by PLP-dependent enzymes (7).

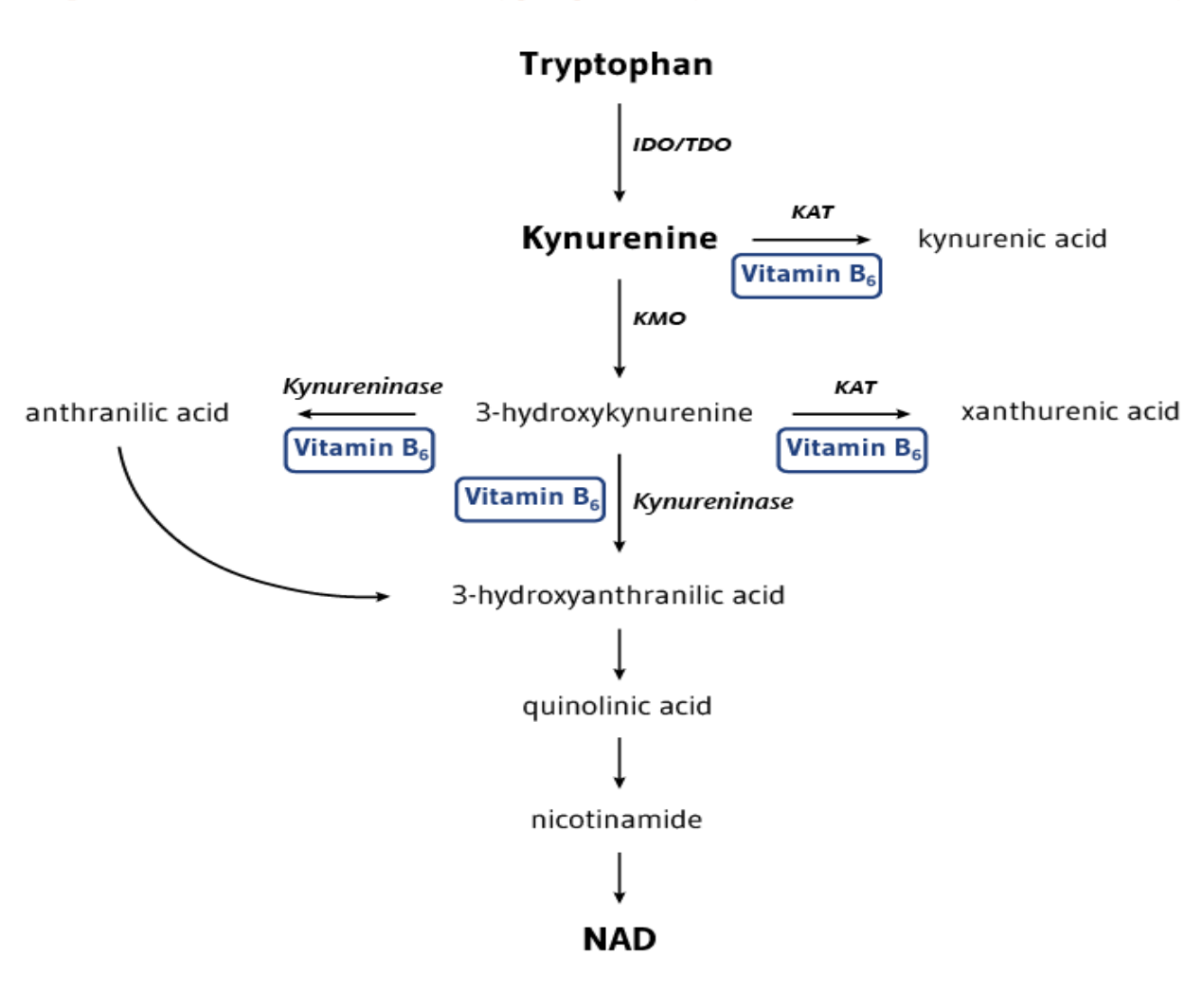
Hemoglobin synthesis and function

PLP functions as a coenzyme of 5-aminolevulinic acid synthase, which is involved in the synthesis of heme, an iron-containing component of hemoglobin. Hemoglobin is found in red blood cells and is critical to their ability to transport oxygen throughout the body. Both pyridoxal and PLP are able to bind to the hemoglobin molecule and affect its ability to pick up and release oxygen. However, the impact of this on normal oxygen delivery to tissues is not known (6, 8). Vitamin B_6 deficiency may impair hemoglobin synthesis and lead to microcytic anemia (3).

Tryptophan metabolism

Deficiency in another B vitamin, niacin, is easily prevented by adequate dietary intakes. The dietary requirement for niacin and the niacin coenzyme, nicotinamide adenine dinucleotide (NAD), can be also met, though to a fairly limited extent, by the catabolism of the essential amino acid tryptophan in the tryptophan-kynurenine pathway (**Figure 2**). Key reactions in this pathway are PLP-dependent; in particular, PLP is the cofactor for the enzyme kynureninase, which catalyzes the conversion of 3-hydroxykynurenine to 3-hydroxyanthranilic acid. A reduction in PLP availability appears to primarily affect kynureninase activity, limiting NAD production and leading to higher concentrations of kynurenine, 3-hydroxykynurenine, and xanthurenic acid in blood and urine (**Figure 2**) (9). Thus, while dietary vitamin B_6 restriction impairs NAD synthesis from tryptophan, adequate PLP levels help maintain NAD formation from tryptophan (10). The effect of vitamin B_6 inadequacy on immune activation and inflammation may be partly related to the role of PLP in the tryptophan-kynurenine metabolism (see Disease Prevention).

Figure 2. Overview of the Tryptophan-Kynurenine Metabolic Pathway



Pyridoxal 5'-phosphate, a vitamin B_6 coenzyme, is required for the activity of key enzymes in the tryptophan catabolic pathway, KAT and kynureninase. Dietary restriction in vitamin B_6 most prominently affects kynureninase activity and results in the shift from 3-hydroxykynurenine metabolism and NAD formation to the production of kynurenic acid and xanthurenic acid. *IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; NAD, nicotinamide adenine dinucleotide; TDO, tryptophan 2,3-dioxygenase*

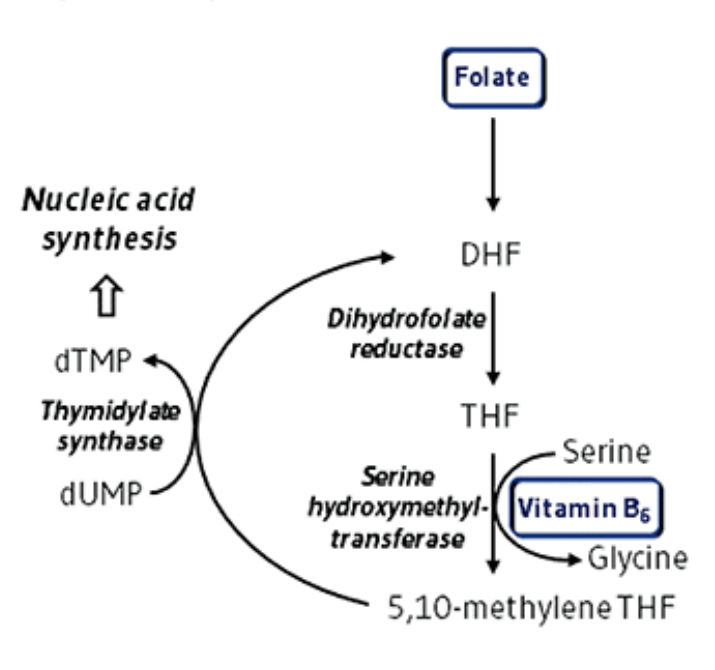
Hormone function

Steroid hormones, such as estrogen and testosterone, exert their effects in the body by binding to steroid hormone receptors in the nucleus of target cells. The nuclear receptors themselves bind to specific regulatory sequences in DNA and alter the transcription of target genes. Experimental studies have uncovered a mechanism by which PLP may affect the activity of steroid receptors and decrease their effects on gene expression. It was found that PLP could interact with RIP140/NRIP1, a repressor of nuclear receptors known for its role in reproductive biology (11). Yet, additional research is needed to confirm that this interaction can enhance RIP140/NRIP1 repressive activity on steroid receptor-mediated gene expression. If the activity of steroid receptors for estrogen, progesterone, testosterone, or other steroid hormones can be inhibited by PLP, it is possible that vitamin B_6 status may influence one's risk of developing diseases driven by steroid hormones, such as breast and prostate cancers (6).

Nucleic acid synthesis

The synthesis of nucleic acids from precursors thymidine and purines is dependent on folate coenzymes. The *de novo* thymidylate (dTMP) biosynthesis pathway involves three enzymes: dihydrofolate reductase (DHFR), serine hydroxymethyltransferase (SHMT), and thymidylate synthase (TYMS) (**Figure 3**). PLP serves as a coenzyme for SHMT, which catalyzes the simultaneous conversions of serine to glycine and tetrahydrofolate (THF) to 5,10-methylene THF. The latter molecule is the one-carbon donor for the generation of dTMP from deoxyuridine monophosphate (dUMP) by TYMS.

Figure 3. *De Novo* Thymidylate Biosynthesis



Folate coenzymes are essential intermediates in the synthesis of nucleic acid precursors thymidine and purines. Thymidylate biosynthesis pathway involves three enzymes: dihydrofolate reductase, serine hydroxymethyltransferase, and thymidylate synthase. Pyridoxal 5'-phosphate (PLP), a vitamin B_6 coenzyme, is required by serine hydroxymethyltransferase, which uses serine as a one-carbon donor for the generation of 5,10-methylenetetrahydrofolate (5,10-methylene THF) from THF. 5,10-methylene THF is then used in both methionine transmethylation cycle (not shown here) and thymidylate biosynthesis. *DHF, dihydrofolate; dUMP, deoxyuridine monophosphate; dTMP, deoxythymidine monophosphate (thymidylate); PLP, pyridoxal 5'-phosphate; THF, tetrahydrofolate.*

Deficiency

Severe deficiency of vitamin B_6 is uncommon. Alcoholics are thought to be most at risk of vitamin B_6 deficiency due to low dietary intakes and impaired metabolism of the vitamin. In the early 1950s, seizures were observed in infants as a result of severe vitamin B_6 deficiency caused by an error in the manufacture of infant formula (7). Abnormal electroencephalogram (EEG) patterns have also been reported in vitamin B_6-deficient adults. Other neurologic symptoms observed in severe vitamin B_6 deficiency include irritability, depression, and confusion; additional symptoms include inflammation of the tongue, sores or ulcers of the mouth, and ulcers of the skin at the corners of the mouth (12).

The Recommended Dietary Allowance (RDA)

Since vitamin B_6 is involved in many aspects of metabolism, especially in amino acid metabolic pathways, an individual's protein intake is likely to influence the requirement for vitamin B_6 (13). Unlike previous recommendations issued by the Food and Nutrition Board (FNB) of the Institute of Medicine, the most recent RDA for vitamin B_6 was not expressed in terms of protein intake, although the relationship was considered in setting the RDA (14). The current RDA was revised by the FNB in 1998 and is presented in **Table 1**.

Table 1. Recommended Dietary Allowance (RDA) for Vitamin B_6

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.1 (AI)	0.1 (AI)
Infants	7-12 months	0.3 (AI)	0.3 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	1.0	1.0
Adolescents	14-18 years	1.3	1.2
Adults	19-50 years	1.3	1.3
Adults	51 years and older	1.7	1.5
Pregnancy	all ages	-	1.9
Breast-feeding	all ages	-	2.0

Disease Prevention

Immune dysfunction

Several enzymatic reactions in the tryptophan-kynurenine pathway are dependent on vitamin B_6 coenzyme, pyridoxal 5'-phosphate (PLP) (see **Figure 2** above) (see Tryptophan metabolism). This pathway is known to be activated during pro-inflammatory immune responses and plays a critical role in immune tolerance of the fetus during pregnancy (15). Key intermediates in the tryptophan-kynurenine pathway are involved in the regulation of immune responses. Several tryptophan derivatives have been found to induce the death (apoptosis) or block the proliferation of certain types of immune cells, such as lymphocytes (in particular T-helper 1). They can also inhibit the production of pro-inflammatory cytokines (reviewed in 15). There is evidence to suggest that adequate vitamin B_6 intake is important for optimal immune system function, especially in older individuals (16, 17). Yet, chronic inflammation that triggers tryptophan degradation and underlies many diseases (e.g., cardiovascular disease and cancers) may precipitate the loss of PLP and increase vitamin B_6 requirements. Additional research is needed to evaluate whether vitamin B_6 intakes higher than the current RDA could prevent and/or reverse immune system impairments (see also Vitamin B_6 and inflammation).

Cardiovascular disease

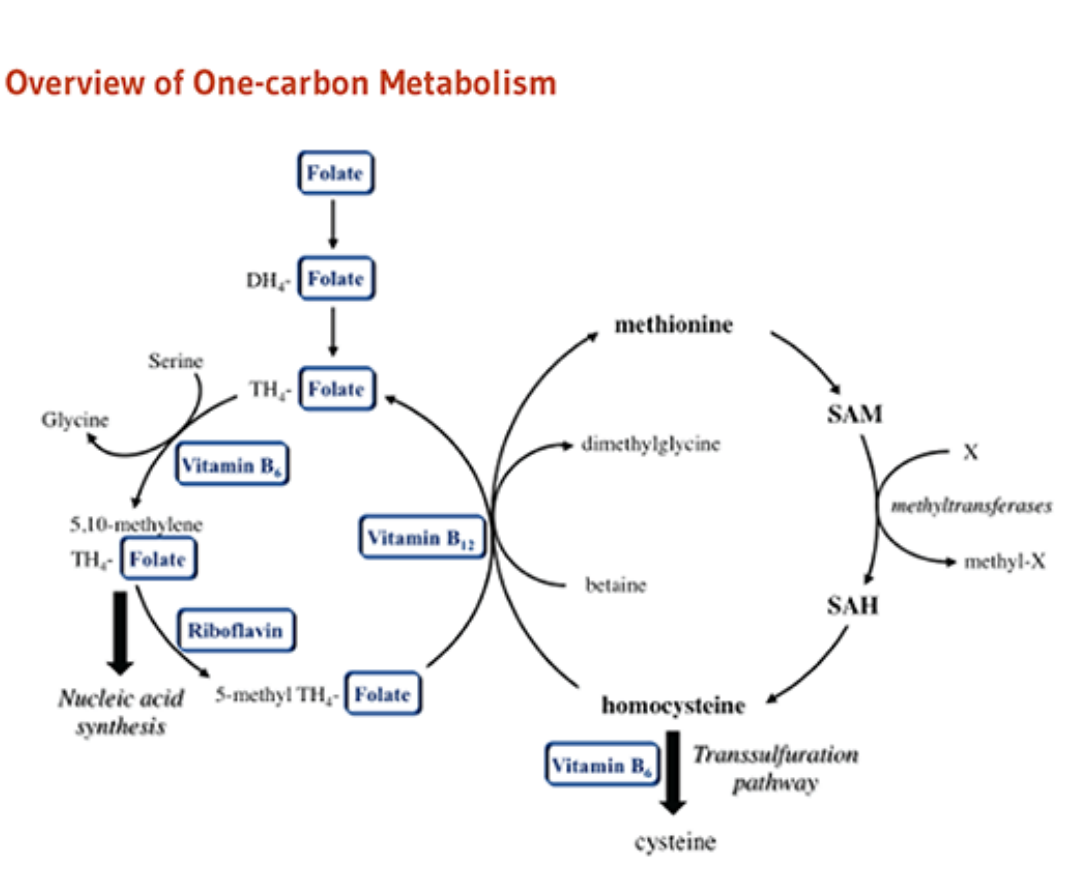
The use of multivitamin supplements (including vitamin B_6) has been associated with a 24% lower risk of incidental coronary artery disease (CAD) in a large prospective study of 80,082 women from the US Nurses' Health Study cohort (18). Using food frequency questionnaires, the authors observed that women in the highest quintile of vitamin B_6 intakes from both food and supplements (median, 4.6 mg/day) had a 34% lower risk of CAD compared to those in the lowest quintile (median, 1.1 mg/day). CAD is characterized by the abnormal stenosis (narrowing) of coronary arteries (generally due to atherosclerosis), which can result in a potentially fatal myocardial infarction (heart attack). More recently, a prospective study that followed a Japanese cohort of over 40,000 middle-aged individuals for 11.5 years reported a 48% lower risk of myocardial infarction in those in the highest (mean, 1.6 mg/day) versus lowest quintile (mean, 1.3 mg/day) of vitamin B_6 intakes in non-supplement users (19).

Early observational studies have also demonstrated an association between suboptimal pyridoxal 5'-phosphate (PLP) plasma level, elevated homocysteine blood level, and increased risk of cardiovascular disease (20-22). More recent research has confirmed that low plasma PLP status is a risk factor for CAD. In a case-control study, which included 184 participants with CAD and 516 healthy controls, low plasma PLP levels (<30 nanomoles/liter) were associated with a near doubling of CAD risk when compared to higher PLP levels (≥30 nanomoles/liter) (23). In a nested case-control study based on the Nurses' Health Study cohort and including 144 cases of myocardial infarction (of which 21 were fatal), women in the highest quartile of blood PLP levels (≥70 nanomoles/liter) had a 79% lower risk of myocardial infarction compared to those in the lowest quartile (<27.9 nanomoles/liter) (24).

Vitamin B_6 and homocysteine

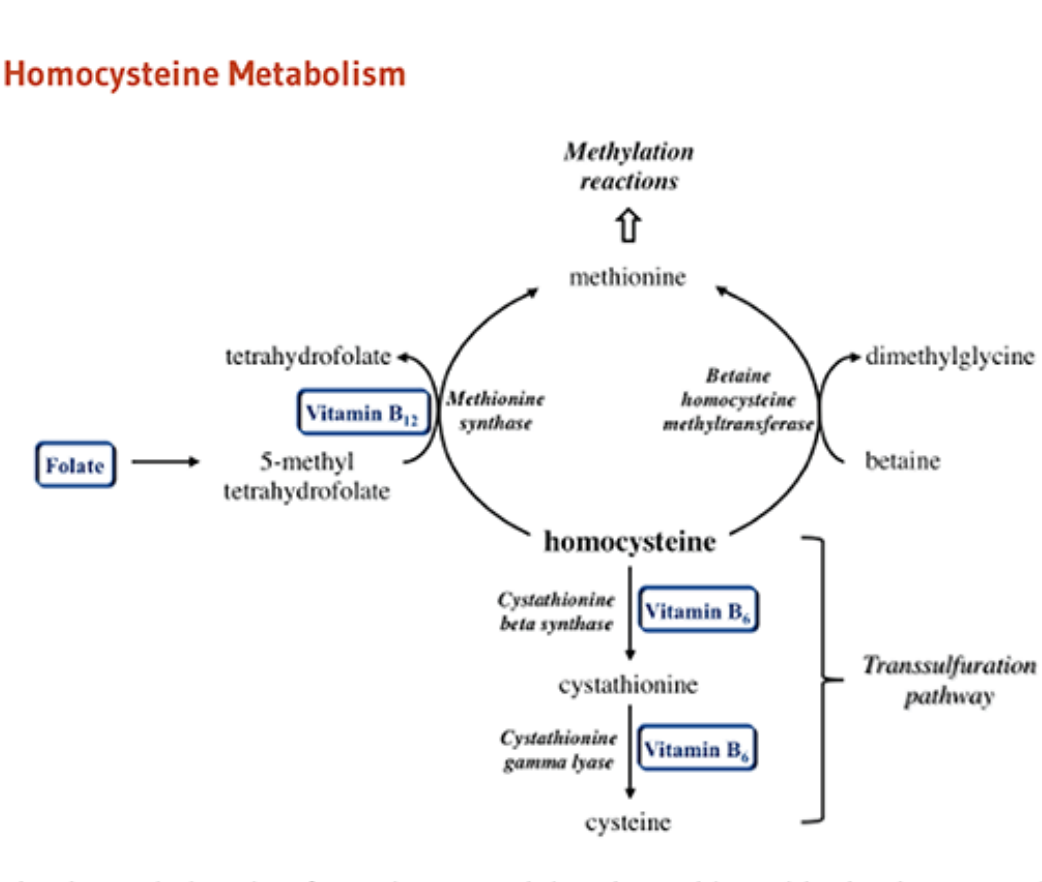
Even moderately elevated levels of homocysteine in the blood have been associated with increased risk for cardiovascular disease (CVD), including cardiac insufficiency (heart failure), CAD, myocardial infarction, and cerebrovascular attack (stroke) (25). During protein digestion, amino acids, including methionine, are released. Methionine is an essential amino acid and precursor of S-adenosylmethionine (SAM), the universal methyl donor for most methylation reactions, including the methylation of DNA, RNA, proteins, and phospholipids (**Figure 4**). Homocysteine is an intermediate in the metabolism of methionine. Healthy individuals utilize two different pathways to regenerate methionine from homocysteine in the methionine remethylation cycle (**Figure 5**). One pathway relies on the vitamin B_{12}-dependent methionine synthase and the methyl donor, 5-methyl tetrahydrofolate (a folate derivative), to convert homocysteine back to methionine. The other reaction is catalyzed by betaine homocysteine methyltransferase, which uses betaine as a source of methyl groups for the formation of methionine from homocysteine. Moreover, two PLP-dependent enzymes are required to convert homocysteine to the amino acid cysteine in homocysteine transsulfuration pathway: cystathionine β synthase and cystathionine γ lyase (**Figure 5**). Thus, the amount of homocysteine in the blood may be influenced by nutritional status of at least three B vitamins, namely folate, vitamin B_{12}, and vitamin B_6.

Figure 4. Overview of One-carbon Metabolism



SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH4-folate, tetrahydrofolate.

Figure 5. Homocysteine Metabolism



Homocysteine is methylated to form the essential amino acid methionine in two pathways. The reaction of homocysteine remethylation catalyzed by the vitamin B_{12}-dependent methionine synthase captures a methyl group from the folate-dependent one-carbon pool (5-methyl tetrahydrofolate). A second pathway requires betaine (N,N,N-trimethylglycine) as a methyl donor for the methylation of homocysteine catalyzed by betaine homocysteine methyltransferase. The catabolic pathway of homocysteine, known as transsulfuration pathway, converts homocysteine to the amino acid cysteine via two vitamin B_6 (PLP)-dependent enzymes: cystathionine β synthase catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionine is then converted to cysteine, α-ketobutyrate, and ammonia by cystathionine γ lyase.

Deficiencies in one or all of these B vitamins may affect both remethylation and transsulfuration processes and result in abnormally elevated homocysteine levels. An early study found that vitamin B_6 supplementation could lower blood homocysteine levels after an oral dose of methionine was given (i.e., a methionine load test) (26), but vitamin B_6 supplementation might not be effective in decreasing fasting levels of homocysteine. In a recent study conducted in nine healthy young volunteers, the rise of homocysteine during the postprandial period (after a meal) was found to be greater with marginal vitamin B_6 deficiency (mean plasma PLP level of 19 nanomoles/liter) as compared to vitamin B_6 sufficiency (mean PLP level of 49 nanomoles/liter) (27). The authors reported an increased rate of cystathionine synthesis with vitamin B_6 restriction, suggesting that homocysteine catabolism in the transsulfuration may be maintained or enhanced in response to a marginal reduction in PLP availability. Yet, the flux ratio between methionine cycle and transsulfuration pathway appeared to favor homocysteine clearance by remethylation rather than transsulfuration in six out of nine participants (27).

Numerous randomized controlled trials, many in subjects with existing hyperhomocysteinemia and vascular dysfunction, have demonstrated that supplementation with folic acid, alone or combined with vitamin B_6 and vitamin B_{12}, could effectively reduce fasting plasma homocysteine concentrations. In 19 intervention studies recently included in a meta-analysis, reductions in homocysteine level in the blood following B-vitamin supplementation ranged between 7.6% and 51.7% compared to baseline levels (28). In contrast, studies supplementing individuals with only vitamin B_6 have usually failed to show an effect on fasting levels of homocysteine (29, 30). Of the three supplemental B vitamins, folic acid appears to be the main determinant in the regulation of fasting homocysteine levels when there is no coexisting deficiency of vitamin B_{12} or vitamin B_6 (31). Yet, the effect of homocysteine lowering on CVD risk reduction is debated. A recent meta-analysis of nine randomized controlled trials reported a 10% reduction in stroke events with supplemental B vitamins, with greater benefits for high-risk subjects (e.g., those with kidney disease) (32). However, most systematic reviews and meta-analyses of B-vitamin intervention studies to date have indicated a lack of causality between the decrease of fasting homocysteine levels and the prevention of cardiovascular events (28, 33-35). Moreover, B-vitamin supplementation trials in high-risk subjects have not resulted in significant changes in carotid intima-media thickness (CIMT) and flow-mediated dilation (FMD) of the brachial artery, two markers of vascular health used to assess atherosclerotic progression (36). Finally, in the Western Norway B Vitamin Intervention Trial (WENBIT), a randomized, double-blind, placebo-controlled trial in 87 subjects with suspected CAD, vitamin B_6 supplementation (40 mg/day of pyridoxine) for a median of 10 months had no effect on coronary stenosis progression, assessed by quantitative angiography (37).

It has been suggested that antiplatelet therapy used in the primary prevention of CVD might interfere with the effect of homocysteine lowering by B vitamins on CVD risk (38). In this context, a post-hoc subgroup analysis of the multicenter, randomized, double blind, placebo-controlled VITATOPS trial (39) proposed that the small benefit of homocysteine-lowering by B vitamins might be cancelled in patients treated with antiplatelet drugs (40). Yet, the benefit of B-vitamin supplementation in primary prevention (i.e., in non-antiplatelet users) remains to be established.

Vitamin B_6 and inflammation

A growing body of evidence currently suggests that low vitamin B_6 status may increase the risk of cardiovascular disease through mechanisms independent of homocysteine lowering (41-43). Markers of immune activation and inflammation have been associated with hyperhomocysteinemia (homocysteine levels >15 micromoles/liter) in individuals with coronary artery disease (CAD) (44). In fact, inflammation is involved in the early steps of atherosclerosis in which lipids deposit in plaques (known as atheromas) within arterial walls and increase the risk of CAD (45). In a case-control study that included 267 patients with CAD and 475 healthy controls, plasma PLP concentrations were inversely correlated with the levels of two markers of systemic inflammation, C-reactive protein (CRP) and fibrinogen (46). Yet, the study suggested that suboptimal PLP levels (<36.3 nanomoles/liter) might contribute to an increased risk of CAD independently of inflammation since the risk was unchanged after adjustment for inflammation markers (unadjusted odds ratio (OR): 1.71 vs. multivariate adjusted OR: 1.73). Furthermore, the analysis of inflammation markers in 2,686 participants of the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 indicated that serum CRP concentrations were inversely related to total vitamin B_6 intakes (from both food and supplements). Specifically, the risk of having serum CRP levels greater than 10 mg/L (corresponding to high inflammatory activity) was 57% higher in individuals with vitamin B_6 intakes lower than 2 mg/day compared to those with intakes equal to and above 5 mg/day (41). In addition, the prevalence of inadequate vitamin B_6 status (plasma PLP levels <20 nanomoles/liter) with intakes lower than 5 mg/day was systematically greater in individuals with high versus low serum CRP concentrations (>10 mg/L vs. ≤3 mg/L), suggesting that inflammation might impair vitamin B_6 metabolism. These observations were confirmed in the study of another cohort (Framingham Offspring Study) in which vitamin B_6 status was linked to an overall inflammatory score based on the levels of 13 inflammation markers (including CRP, fibrinogen, tumor necrosis factor-α, and interleukin-6) (42). Specifically, plasma PLP levels were 24% lower in individuals in the highest versus lowest tertile of inflammatory score. Moreover, the inverse correlation between PLP levels and inflammatory scores remained significant regardless of vitamin B_6 intakes, questioning again the nature of this relationship. Interestingly, a recent analysis of data collected in the WENBIT study demonstrated that systemic inflammation was associated with an increased degradation of pyridoxal (PL) to 4-pyridoxic acid (PA), supporting the use of the ratio PA:(PL+PLP) as a marker of both vitamin B_6 status and systemic inflammation (47). Finally, while inflammation may contribute to lower vitamin B_6 status, current evidence fails to support a role for vitamin B_6 in the control of inflammation in patients with cardiovascular disease (48, 49).

Cognitive decline and Alzheimer's disease

A few observational studies have linked cognitive decline and Alzheimer's disease (AD) in the elderly with inadequate status of folate, vitamin B_{12}, and vitamin B_6 (50). Yet, the relationship between B vitamins and cognitive health in aging is complicated by both the high prevalence of hyperhomocysteinemia and signs of systemic inflammation in elderly people (51). On the one hand, since inflammation may impair vitamin B_6 metabolism, low serum PLP levels may well be caused by processes related to aging rather than by malnutrition. On the other hand, high serum homocysteine may possibly be a risk factor for cognitive decline in the elderly, although the matter remains under debate. Specifically, the meta-analysis of 19 randomized, placebo-controlled trials of B-vitamin supplementation failed to report any difference in several measures of cognitive function between treatment and placebo groups, despite the treatment effectively lowering homocysteine levels (52). In a recent randomized, double-blind, placebo-controlled study of 2,695 stroke survivors with or without cognitive impairments, daily supplementation with 2 mg of folic acid, 0.5 mg of vitamin B_{12}, and 25 mg of vitamin B_6 for 3.4 years resulted in significant reductions in mean homocysteine levels (by 28% and 43% in cognitively unimpaired and impaired patients, respectively) compared to placebo. Yet, the B-vitamin intervention had no effect on either the incidence of newly diagnosed cognitive impairments or on measures of cognitive performance when compared to placebo (53). In contrast, another recent placebo-controlled trial found that a daily B-vitamin regimen that led to significant homocysteine lowering in high-risk elderly individuals could limit the progressive atrophy of gray matter brain regions associated with the AD process (54). Yet, the authors attributed the changes in homocysteine levels primarily to vitamin B_{12}. Because of mixed findings, it is presently unclear whether supplementation with B vitamins might blunt cognitive decline in the elderly. Evidence is needed to determine whether marginal B-vitamin deficiencies, which are relatively common in the elderly, even contribute to age-associated declines in cognitive function, or whether both result from processes associated with aging and/or disease.

Depression

Late-life depression is a common disorder sometimes occurring after acute illnesses, such as hip fracture or stroke (55, 56). Coexistence of symptoms of depression and low vitamin B_6 status (plasma PLP level ≤20 nanomoles/liter) has been reported in a few cross-sectional studies (57, 58). In a prospective study of 3,503 free-living people aged 65 and older from the Chicago Health and Aging Project, total vitamin B_6 intakes (but not dietary intakes alone) were inversely correlated with the incidence of depressive symptoms during a mean follow-up period of 7.2 years (59). In a randomized, double-blind, placebo-controlled trial in 563 individuals who suffered from a recent stroke, daily supplementation of 2 mg of folic acid, 0.5 mg of vitamin B_{12}, and 25 mg of vitamin B_6 halved the risk of developing a major depressive episode during a mean follow-up period of 7.1 years (60). This reduction in risk was associated with a 25% lower level of plasma homocysteine in supplemented patients compared to controls. Additional evidence is needed to evaluate whether B vitamins could be included in the routine management of older people at high risk for depression.

Cancer

Chronic inflammation that underlies most cancers may enhance vitamin B_6 degradation (see Vitamin B_6 and inflammation). In addition, because PLP is required for the methionine cycle, homocysteine catabolism, and thymidylate synthesis, low vitamin B_6 status might affect these pathways and potentially increase the risk for chronic conditions. The systematic review of nine prospective studies found either inverse or positive associations between vitamin B_6 intakes and colorectal cancer (CRC) risk (61). Inconsistent evidence regarding the link between vitamin B_6 intakes and breast cancer was also recently reported in a meta-analysis (62). Yet, a prospective study that followed nearly 500,000 older adults for nine years observed that the risk of esophageal and stomach cancers was lower in participants in the highest versus lowest quintile of total vitamin B_6 intakes (median values, 2.7 mg/day vs. 1.4 mg/day) (63). Additionally, a meta-analysis of four nested case-control studies reported a 48% reduction in CRC risk in the highest versus lowest quartile of blood PLP level (61). Another meta-analysis of five nested case-control studies found higher versus lower serum PLP levels to be associated with a 29% lower risk of breast cancer in postmenopausal, but not premenopausal, women (62).

Very few randomized, placebo-controlled trials investigating the nature of the association between B vitamins and cancer risk have focused on vitamin B_6. Two earlier studies conducted in subjects with coronary artery disease failed to observe any benefit of supplemental vitamin B_6 (40 mg/day) on CRC risk and mortality (reviewed in 64). A recent randomized, double-blind, placebo-controlled study conducted in 1,470 women with high cardiovascular risk showed that daily supplementation with 2.5 mg of folic acid, 1 mg of vitamin B_{12}, and 50 mg of vitamin B_6 for a mean treatment period of 7.3 years had no effect on the risk of developing colorectal adenoma when compared to placebo (65).

Kidney stones

A large prospective study examined the relationship between vitamin B_6 intake and the occurrence of symptomatic kidney stones in women. A group of more than 85,000 women without a prior history of kidney stones were followed over 14 years, and those who consumed 40 mg or more of vitamin B_6 daily had only two-thirds the risk of developing kidney stones compared with those who consumed 3 mg or less (66). However, in a group of more than 45,000 men followed for 14 years, no association was found between vitamin B_6 intake and the occurrence of kidney stones (67). Limited experimental data have suggested that supplementation with high doses of pyridoxamine may help decrease the formation of calcium oxalate kidney stones and reduce urinary oxalate levels, an important determinant of calcium oxalate kidney stone formation (68, 69). Presently, the relationship between vitamin B_6 intake and the risk of developing kidney stones requires further study before any recommendations can be made.

Disease Treatment

Vitamin B_6 supplements at pharmacologic doses (i.e., doses much larger than those needed to prevent deficiency) have been used in an attempt to treat a wide variety of conditions, some of which are discussed below.

Metabolic diseases

A few rare inborn metabolic disorders, including pyridoxine-dependent epilepsy (PDE) and pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, are the cause of early-onset epileptic encephalopathies that are found to be responsive to pharmacologic doses of vitamin B_6. In individuals affected by PDE and PNPO deficiency, PLP bioavailability is limited, and treatment with pyridoxine and/or PLP have been used to alleviate or abolish epileptic seizures characterizing these conditions (70, 71). Pyridoxine therapy, along with dietary protein restriction, is also used in the management of vitamin B_6 responsive homocystinuria caused by the deficiency of the PLP-dependent enzyme, cystathionine β synthase (72).

Morning sickness

Nausea and vomiting in pregnancy (NVP), often referred to as morning sickness, can affect up to 85% of women during early pregnancy and usually lasts between 12 and 16 weeks (73). Vitamin B_6 has been used since the 1940s to treat nausea during pregnancy. Vitamin B_6 was originally included in the medication Bendectin, which was prescribed for NVP treatment and later withdrawn from the market due to unproven concerns that it increased the risk for birth defects. Vitamin B_6 itself is considered safe during pregnancy and has been used in pregnant women without any evidence of fetal harm (74). The results of two double-blind, placebo-controlled trials, including 401 pregnant women that used 25 mg of pyridoxine every eight hours for three days (75) or 10 mg of pyridoxine every eight hours for five days (76), suggested that vitamin B_6 may be beneficial in reducing nausea. A recent systematic review of randomized controlled trials on NVP symptoms during early pregnancy found supplemental vitamin B_6 to be somewhat effective (77). It should be noted that NVP usually resolves without any treatment, making it difficult to perform well-controlled trials. More recently, NVP symptoms were evaluated using Pregnancy Unique Quantification of Emesis (PUQE) scores in a randomized, double-blind, placebo-controlled study conducted in 256 pregnant women (7-14 weeks' gestation) suffering from NVP (78). Supplementation with pyridoxine and the drug doxylamine significantly improved NVP symptoms, as assessed by lower PUQE scores compared to placebo. Moreover, more women supplemented with pyridoxine-doxylamine (48.9%) than placebo-treated (32.8%) asked to continue their treatment at the end of the 15-day trial. The American and Canadian Colleges of Obstetrics and Gynecology have recommended the use of vitamin B_6 (pyridoxine hydrochloride, 10 mg) and doxylamine succinate (10 mg) as first-line therapy for NVP (73).

Premenstrual syndrome

Premenstrual syndrome (PMS) refers to a cluster of symptoms, including but not limited to fatigue, irritability, moodiness/depression, fluid retention, and breast tenderness, that begin sometime after ovulation (mid-cycle) and subside with the onset of menstruation (the monthly period). A systematic review and meta-analysis of nine randomized, placebo-controlled trials suggested that supplemental vitamin B_6, up to 100 mg/day, may be of value to treat PMS, including mood symptoms; however, only limited conclusions could be drawn because most of the studies were of poor quality (79). Another more recent review of 13 randomized controlled studies also emphasized the need for conclusive evidence before recommendations can be made (80).

Depression

The importance of PLP-dependent enzymes in the synthesis of several neurotransmitters (see Nervous system function) has led researchers to consider whether vitamin B_6 deficiency may contribute to the onset of depressive symptoms (see Disease Prevention). There is limited evidence suggesting that supplemental vitamin B_6 may have therapeutic efficacy in the management of depression. In a randomized, placebo-controlled trial conducted in 225 elderly patients hospitalized for acute illness, a six-month intervention with daily multivitamin/mineral supplements improved nutritional B-vitamin status and decreased the number and severity of depressive symptoms when compared to placebo (81). In addition, while supplement intake effectively reduced plasma homocysteine levels compared to placebo, the effect of supplementation on depressive symptoms at the end of the trial was greater in treated subjects in the lowest versus highest quartile of homocysteine levels (≤10 micromoles/liter vs. ≥16.1 micromoles/liter) (82). Yet, the etiology of late-onset depression is unclear and evidence is currently lacking to suggest whether supplemental B vitamins (including vitamin B_6) could relieve depressive symptoms.

Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) causes numbness, pain, and weakness of the hand and fingers due to compression of the median nerve at the wrist. It may result from repetitive stress injury of the wrist or from soft-tissue swelling, which sometimes occurs with pregnancy or hypothyroidism. Early studies by the same investigator suggested that supplementation with 100-200 mg/day of vitamin B_6 for several months might improve CTS symptoms in individuals with low vitamin B_6 status (83, 84). In addition, a cross-sectional study in 137 men not taking vitamin supplements found that decreased blood levels of PLP were associated with increased pain, tingling, and nocturnal awakening—all symptoms of CTS (85). However, studies using electrophysiological measurements of median nerve conduction have largely failed to find an association between vitamin B_6 deficiency and CTS (86). While a few studies have noted some symptomatic relief with vitamin B_6 supplementation, double-blind, placebo-controlled trials have not generally found vitamin B_6 to be effective in treating CTS (86). Yet, despite its equivocal effectiveness, vitamin B_6 supplementation is sometimes used in complementary therapy in an attempt to avoid hand surgery. Patients taking high doses of vitamin B_6 should be advised by a physician and monitored for vitamin B_6-related toxicity symptoms (see Toxicity) (87).

Sources

Food sources

The analysis of data collected in the US NHANES 2003-2004 has indicated that vitamin B_6 intakes from food only averaged about 1.9 mg/day (88). Yet, despite values well above the current RDA, total vitamin B_6 intakes (combining food and supplements) below 2 mg/day appear to be associated with relatively high proportions of low vitamin B_6 status in all age groups (see Supplements). Many plant foods contain a unique form of vitamin B_6 called pyridoxine glucoside; this form of vitamin B_6 appears to be only about half as bioavailable as vitamin B_6 from other food sources or supplements (7). Vitamin B_6 in a mixed diet has been found to be approximately 75% bioavailable (14). In most cases, including foods in the diet that are rich in vitamin B_6 should supply enough to meet the current RDA. However, those who follow a very restricted vegetarian diet might need to increase their vitamin B_6 intake by eating foods fortified with vitamin B_6 or by taking a supplement. Some foods that are relatively rich in vitamin B_6 and their vitamin B_6 content in milligrams (mg) are listed in **Table 2**. For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin B_6

Food	Serving	Vitamin B_6 (mg)
Fortified breakfast cereal	1 cup	0.5-2.5
Salmon, wild (cooked)	3 ounces*	0.48-0.80
Potato, Russet, with skin (baked)	1 medium	0.70
Turkey, light meat (cooked)	3 ounces	0.69
Avocado	1 medium	0.52
Chicken, light meat without skin (cooked)	3 ounces	0.51
Spinach (cooked)	1 cup	0.44
Banana	1 medium	0.43
Dried plums, pitted	1 cup	0.36
Hazelnuts (dry roasted)	1 ounce	0.18
Vegetable juice cocktail	6 ounces	0.13
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Supplements

Vitamin B_6 is available as pyridoxine hydrochloride in multivitamin, vitamin B-complex, and vitamin B_6 supplements (89). In NHANES 2003-2004, low vitamin B_6 status (plasma PLP level <20 nanomoles/liter) was reported in 24% of non users of supplements and 11% of supplement users. Moreover, total vitamin B_6 intakes (from food and supplements) lower than 2 mg/day were associated with high proportions of low plasma PLP levels: 16% in men aged 13-54 years, 24% in menstruating women, and 26% in individuals aged 65 years and older. Finally, the prevalence of low PLP levels was found to be greater in individuals consuming less than 2 mg/day of vitamin B_6 compared to higher intakes. For example, only 14% of men and women aged 65 and older had low PLP values with total vitamin B_6 intakes of 2-2.9 mg/day compared to 26% in those consuming less than 2 mg/day of vitamin B_6 (88).

Safety

Toxicity

Because adverse effects have only been documented from vitamin B_6 supplements and never from food sources, safety concerning only the supplemental form of vitamin B_6 (pyridoxine) is discussed. Although vitamin B_6 is a water-soluble vitamin and is excreted in the urine, long-term supplementation with very high doses of pyridoxine may result in painful neurological symptoms known as sensory neuropathy. Symptoms include pain and numbness of the extremities and in severe cases, difficulty walking. Sensory neuropathy typically develops at doses of pyridoxine in excess of 1,000 mg per day. However, there have been a few case reports of individuals who developed sensory neuropathies at doses of less than 500 mg daily over a period of months. Yet, none of the studies in which an objective neurological examination was performed reported evidence of sensory nerve damage at intakes below 200 mg pyridoxine daily (90). To prevent sensory neuropathy in virtually all individuals, the Food and Nutrition Board of the Institute of Medicine set the tolerable upper intake level (UL) for pyridoxine at 100 mg/day for adults (**Table 3**) (14). Because placebo-controlled studies have generally failed to show therapeutic benefits of high doses of pyridoxine, there is little reason to exceed the UL of 100 mg/day.

Table 3. Tolerable Upper Intake Level (UL) for Vitamin B_6

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	30
Children 4-8 years	40
Children 9-13 years	60
Adolescents 14-18 years	80
Adults 19 years and older	100
*Source of intake should be from food and formula only.	

Drug interactions

Certain medications interfere with the metabolism of vitamin B_6; therefore, some individuals may be vulnerable to a vitamin B_6 deficiency if supplemental vitamin B_6 is not taken. In the NHANES 2003-2004 analysis, significantly more current and past users of oral contraceptives (OCs) among menstruating women had low plasma PLP levels compared to women who have never used OCs, suggesting that the estrogen content of OCs may interfere with vitamin B_6 metabolism (see Side effects of oral contraceptives) (88). Anti-tuberculosis medications (e.g., isoniazid and cycloserine), the metal chelator penicillamine, and anti-parkinsonian drugs like L-Dopa can all form complexes with vitamin B_6 and limit its bioavailability, thus creating a functional deficiency. PLP bioavailability may also be reduced by methylxanthines, such as theophylline used to treat certain respiratory conditions (7). The long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs; e.g. celecoxib and naproxen) may also impair vitamin B_6 metabolism (91). Conversely, high doses of vitamin B_6 have been found to decrease the efficacy of two anticonvulsants, phenobarbital and phenytoin, and of L-Dopa (6, 90).

Side effects of oral contraceptives

Because vitamin B_6 is required for the metabolism of the amino acid tryptophan, the tryptophan load test (an assay of tryptophan metabolites after an oral dose of tryptophan) has been used as a functional assessment of vitamin B_6 status. Abnormal tryptophan load tests in women taking high-dose oral contraceptives (OCs) in the 1960s and 1970s suggested that these women were vitamin B_6 deficient, which led to the prescription of high doses of vitamin B_6 (100-150 mg/day) to women taking OCs. However, most other indices of vitamin B_6 status were normal in women on high-dose OCs, and the estrogen content of OCs appeared to be more likely responsible for the abnormality in tryptophan metabolism (88). Yet, more recently, the use of lower dose formulations has also been associated with vitamin B_6 inadequacy (88, 92). Although it is not known whether OCs actually impair vitamin B_6 metabolism or merely affect the tissue distribution of PLP, the use of OCs may place women at higher risk of vitamin B_6 deficiency when they discontinue OCs and become pregnant (93). Whether OC users are at higher risk of cardiovascular disease despite normal homocysteine levels also needs to be determined. Finally, although high doses of vitamin B_6 (pyridoxine) have demonstrated no benefit in preventing the risk of side effects from OCs (94), the use of vitamin B_6 supplements may be warranted in current and past OC users.

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the RDA for vitamin B_6. LPI recommends that all adults take a daily multivitamin/mineral supplement, which usually contains at least 2 mg of vitamin B_6. This amount is slightly above the RDA but still 50 times lower than the tolerable upper intake level (UL) set by the Food and Nutrition Board (see Safety).

Older adults (>50 years)

Early metabolic studies have indicated that the requirement for vitamin B_6 in older adults is approximately 2 mg daily (95). Yet, the analysis of the US population survey (NHANES) 2003-2004 showed that adequate vitamin B_6 status and low homocysteine levels were associated with total vitamin B_6 intakes equal to and above 3 mg/day in people aged 65 years and older (88). The Linus Pauling Institute recommends that older adults take a multivitamin/mineral supplement, which provides at least 2.0 mg of vitamin B_6 daily.

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Vitamin B12

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Summary

- Vitamin B_{12} or cobalamin plays essential roles in folate metabolism and in the synthesis of the citric acid cycle intermediate, succinyl-CoA. *(More information)*
- Vitamin B_{12} deficiency is commonly associated with chronic stomach inflammation, which may contribute to an autoimmune vitamin B_{12} malabsorption syndrome called pernicious anemia and to a food-bound vitamin B_{12} malabsorption syndrome. Impairment of vitamin B_{12} absorption can cause megaloblastic anemia and neurologic disorders in deficient subjects. *(More information)*
- Normal function of the digestive system required for food-bound vitamin B_{12} absorption is commonly impaired in individuals over 60 years of age, placing them at risk for vitamin B_{12} deficiency. *(More information)*
- Vitamin B_{12} and folate are important for homocysteine metabolism. Elevated homocysteine levels in blood are a risk factor for cardiovascular disease (CVD). Although B vitamin supplementation has been proven effective to control homocysteine levels, current data from intervention trials have not shown that lowering homocysteine levels decreases CVD risk. *(More information)*
- The preservation of DNA integrity is dependent on folate and vitamin B_{12} availability. Poor vitamin B_{12} status has been linked to increased risk of breast cancer in some, but not all, observational studies. There is a need to evaluate whether supplemental vitamin B_{12}, along with folic acid, could help reduce breast cancer incidence. *(More information)*
- Low maternal vitamin B_{12} status has been associated with an increased risk of neural tube defects (NTD), but it is not known whether vitamin B_{12} supplementation could help reduce the risk of NTD. *(More information)*
- Vitamin B_{12} is essential for the preservation of the myelin sheath around neurons and for the synthesis of neurotransmitters. While hyperhomocysteinemia may increase the risk of cognitive impairment, it is not clear whether vitamin B_{12} deficiency contributes to the risk of dementia in the elderly. Although B-vitamin supplementation lowers homocysteine levels in older subjects, the long-term benefit is not yet known. *(More information)*
- Both depression and osteoporosis have been linked to diminished vitamin B_{12} status and high homocysteine levels. *(More information)*
- Products of animal origin constitute the primary source of vitamin B_{12}. Older individuals and vegans are advised to use vitamin B_{12} fortified foods and supplements to meet their needs. *(More information)*
- The long-term use of certain medications, such as inhibitors of stomach acid secretion, can adversely affect vitamin B_{12} absorption. *(More information)*

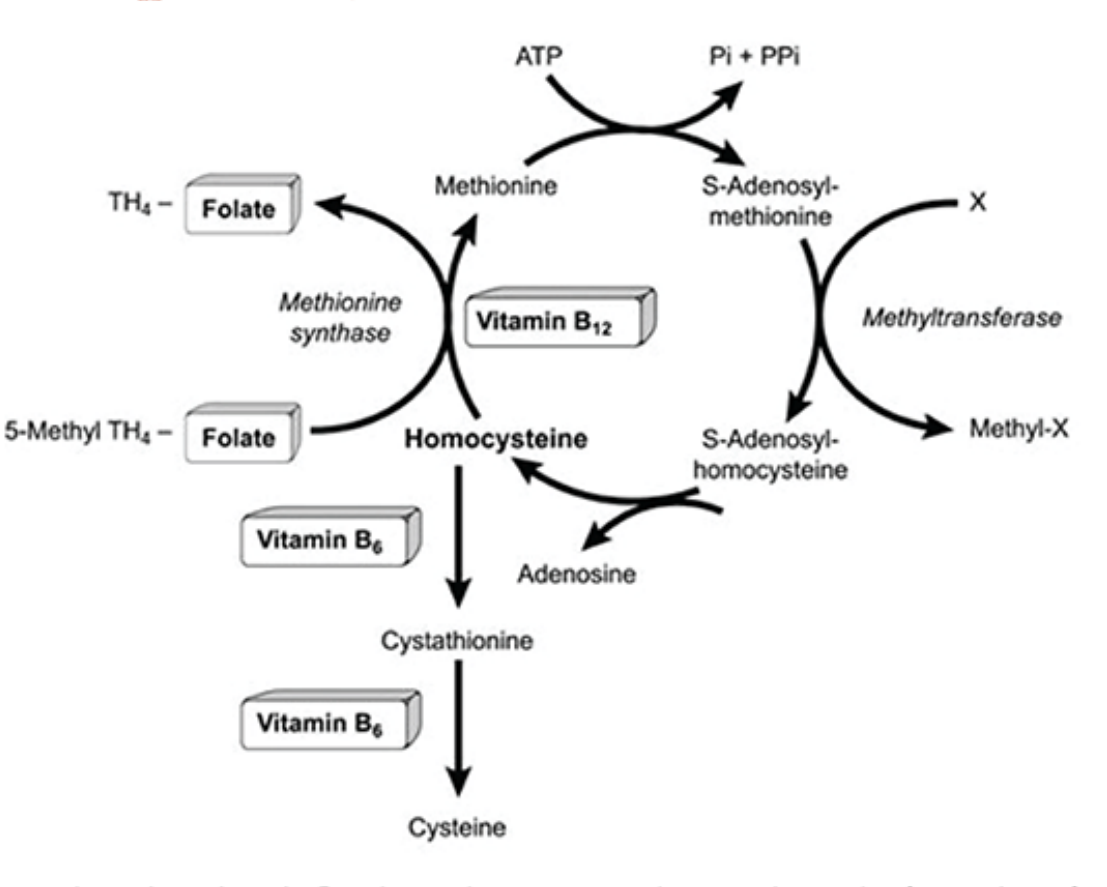
Vitamin B_{12} has the largest and most complex chemical structure of all the vitamins. It is unique among vitamins in that it contains a metal ion, cobalt. For this reason cobalamin is the term used to refer to compounds having vitamin B_{12} activity. Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of vitamin B_{12} used in the human body (1). The form of cobalamin used in most nutritional supplements and fortified foods, cyanocobalamin, is readily converted to 5-deoxyadenosylcobalamin and methylcobalamin in the body. In mammals, cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-coenzyme A mutase (2).

Function

Cofactor for methionine synthase

Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of the amino acid, methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA, RNA, and proteins (3). Aberrant methylation of DNA and proteins, which causes alterations in chromatin structure and gene expression, are a common feature of cancer cells. Inadequate function of methionine synthase can lead to an accumulation of homocysteine, which has been associated with increased risk of cardiovascular disease (**Figure 1**).

Figure 1. Vitamin B_{12} and Homocysteine Metabolism

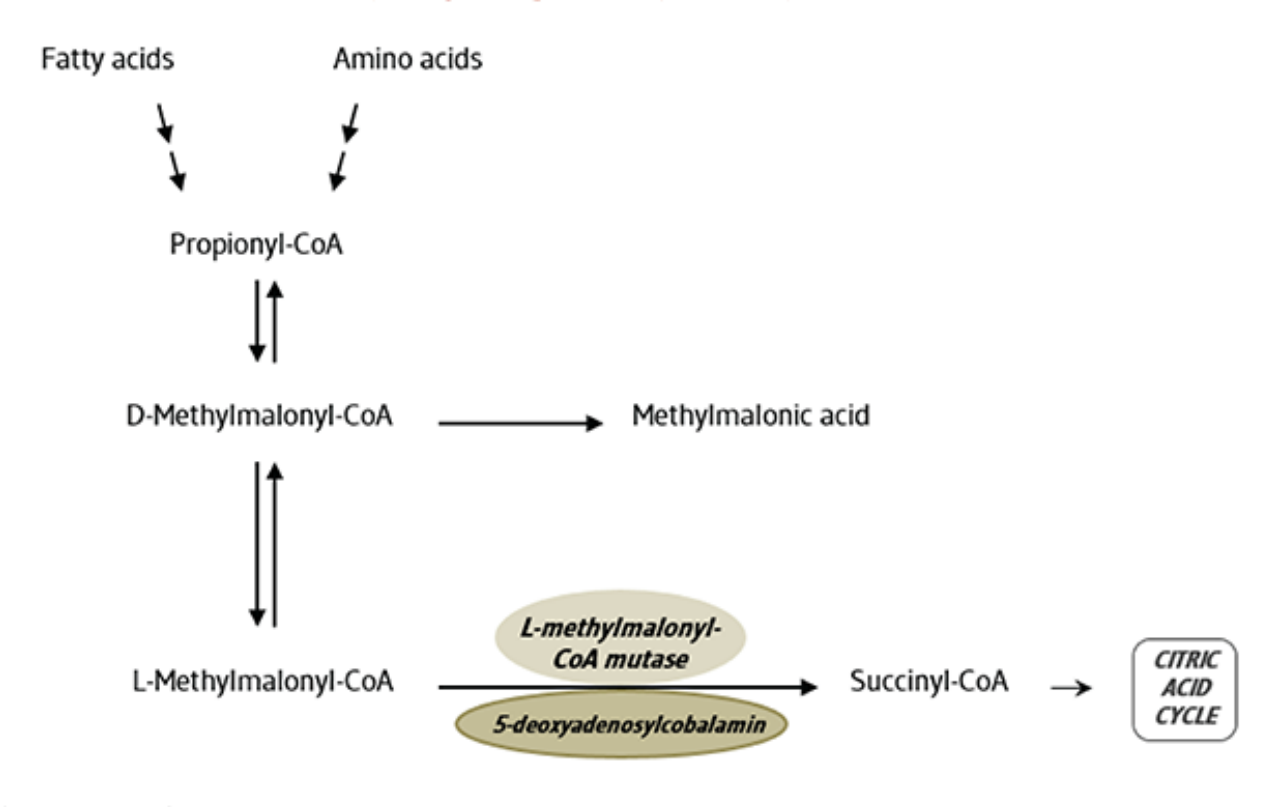


Methionine synthase is a vitamin B_{12}-dependent enzyme that catalyzes the formation of methionine from homocysteine using 5-methyltetrahydrofolate (5-methyl TH_4), a folate derivative, as a methyl donor. Another pathway catalyzed by betaine homocysteine methyltransferase also remethylates homocysteine to methionine using betaine as a methyl donor (not shown here). Methionine, in the form of S-adenosylmethionine, is required for most biological methylation reactions, including DNA methylation.

Cofactor for L-methylmalonyl-coenzyme A mutase

5-Deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl-coenzyme A to succinyl-coenzyme A (succinyl-CoA), which then enters the citric acid cycle (**Figure 2**). Succinyl-CoA plays an important role in the production of energy from lipids and proteins and is also required for the synthesis of hemoglobin, the oxygen-carrying pigment in red blood cells (3).

Figure 2. Metabolic Pathway Requiring 5-deoxyadenosylcobalamin



CoA, coenzyme A.

Deficiency

In healthy adults, vitamin B_{12} deficiency is uncommon, mainly because total body stores can exceed 2,500 μg, daily turnover is slow, and dietary intake of only 2.4 μg/day is sufficient to maintain adequate vitamin B_{12} status (see RDA) (4). In elderly individuals, vitamin B_{12} deficiency is more common mainly because of impaired intestinal absorption that can result in marginal to severe vitamin B_{12} deficiency in this population.

Causes of vitamin B_{12} deficiency

Intestinal malabsorption, rather than inadequate dietary intake, can explain most cases of vitamin B_{12} deficiency (5). Absorption of vitamin B_{12} from food requires normal function of the stomach, pancreas, and small intestine. Stomach acid and enzymes free vitamin B_{12} from food, allowing it to bind to R-protein (also known as transcobalamin-1 or haptocorrin), found in saliva and gastric fluids. In the alkaline environment of the small intestine, R-proteins are degraded by pancreatic enzymes, freeing vitamin B_{12} to bind to intrinsic factor (IF), a protein secreted by specialized cells in the stomach. Receptors on the surface of the ileum (final part of the small intestine) take up the IF-B_{12} complex only in the presence of calcium, which is supplied by the pancreas (5). Vitamin B_{12} can also be absorbed by passive diffusion, but this process is very inefficient—only about 1% absorption of the vitamin B_{12} dose is absorbed passively (2). The prevalent causes of vitamin B_{12} deficiency are (1) an autoimmune condition known as pernicious anemia, and (2) a disorder called food-bound vitamin B_{12} malabsorption. Both conditions have been associated with a chronic inflammatory disease of the stomach known as atrophic gastritis.

Atrophic gastritis

Atrophic gastritis is thought to affect 10%-30% of people over 60 years of age (6). The condition is frequently associated with the presence of autoantibodies directed toward stomach cells (see Pernicious anemia) and/or infection by the bacteria, *Helicobacter pylori* (*H. pylori*) (7). *H. pylori* infection induces chronic inflammation of the stomach, which may progress to peptic ulcer disease, atrophic gastritis, and/or gastric cancer in some individuals. Diminished gastric function in individuals with atrophic gastritis can result in bacterial overgrowth in the small intestine and cause food-bound vitamin B_{12} malabsorption. Vitamin B_{12} levels in serum, plasma, and gastric fluids are significantly decreased in individuals with *H. pylori* infection, and eradication of the bacteria has been shown to significantly improve vitamin B_{12} serum concentrations (8).

Pernicious anemia

Pernicious anemia has been estimated to be present in approximately 2% of individuals over 60 years of age (9). Although anemia is often a symptom, the condition is actually the end stage of an autoimmune inflammation of the stomach known as autoimmune atrophic gastritis, resulting in destruction of stomach cells by one's own antibodies (autoantibodies). Progressive destruction of the cells that line the stomach causes decreased secretion of acid and enzymes required to release food-bound vitamin B_{12}. Antibodies to intrinsic factor (IF) bind to IF preventing formation of the IF-B_{12} complex, further inhibiting vitamin B_{12} absorption. About 20% of the relatives of pernicious anemia patients also have the condition, suggesting a genetic predisposition. It is also thought that *H. pylori* infection could be involved in initiating the autoimmune response in a subset of individuals (10). Further, co-occurrence of autoimmune atrophic gastritis with other autoimmune conditions, especially autoimmune thyroiditis and type 1 diabetes mellitus, has been reported (11, 12).

Treatment of pernicious anemia generally requires injections of vitamin B_{12} to bypass intestinal absorption. High-dose oral supplementation is another treatment option, because consuming 1,000 μg (1 mg)/day of vitamin B_{12} orally should result in the absorption of about 10 μg/day (1% of dose) by passive diffusion. In fact, high-dose oral therapy is considered to be as effective as intramuscular injection (4).

Food-bound vitamin B_{12} malabsorption

Food-bound vitamin B_{12} malabsorption is defined as an impaired ability to absorb food- or protein-bound vitamin B_{12}; individuals with this condition can fully absorb the free form (13). While the condition is the major cause of poor vitamin B_{12} status in the elderly population, it is usually associated with atrophic gastritis, a chronic inflammation of the lining of the stomach that ultimately results in the loss of glands in the stomach (atrophy) and decreased stomach acid production (see Atrophic gastritis). Because stomach acid is required for the release of vitamin B_{12} from the proteins in food, vitamin B_{12} absorption is diminished. Decreased stomach acid production also provides an environment conducive to the overgrowth of anaerobic bacteria in the stomach, which further interferes with vitamin B_{12} absorption (3). Because vitamin B_{12} in supplements is not bound to protein, and because intrinsic factor (IF) is still available, the absorption of supplemental vitamin B_{12} is not reduced as it is in pernicious anemia. Thus, individuals with food-bound vitamin B_{12} malabsorption do not have an increased requirement for vitamin B_{12}; they simply need it in the crystalline form found in fortified foods and dietary supplements.

Other causes of vitamin B_{12} deficiency

Other causes of vitamin B_{12} deficiency include surgical resection of the stomach or portions of the small intestine where receptors for the IF-B_{12} complex are located. Conditions affecting the small intestine, such as malabsorption syndromes (celiac disease and tropical sprue), may also result in vitamin B_{12} deficiency. Because the pancreas provides critical enzymes, as well as calcium required for vitamin B_{12} absorption, pancreatic insufficiency may contribute to vitamin B_{12} deficiency. Since vitamin B_{12} is found only in foods of animal origin, a strict vegetarian (vegan) diet has resulted in cases of vitamin B_{12} deficiency. Moreover, alcoholics may experience reduced intestinal absorption of vitamin B_{12} (2), and individuals with acquired immunodeficiency syndrome (AIDS) appear to be at increased risk of deficiency, possibly related to a failure of the IF-B_{12} receptor to take up the IF-B_{12} complex (3). Further, long-term use of acid-reducing drugs has also been implicated in vitamin B_{12} deficiency (see Drug interactions).

Inherited disorders of vitamin B_{12} absorption

Rare cases of inborn errors of vitamin B_{12} metabolism have been reported in the literature (reviewed in 5). Imerslund-Gräsbeck syndrome is an inherited vitamin B_{12} malabsorption syndrome that causes megaloblastic anemia and neurologic disorders of variable severity in affected subjects. Similar clinical symptoms are found in individuals with hereditary IF deficiency (also called congenital pernicious anemia) in whom the lack of IF results in the defective absorption of vitamin B_{12}. Additionally, mutations affecting vitamin B_{12} transport in the body have been identified (14).

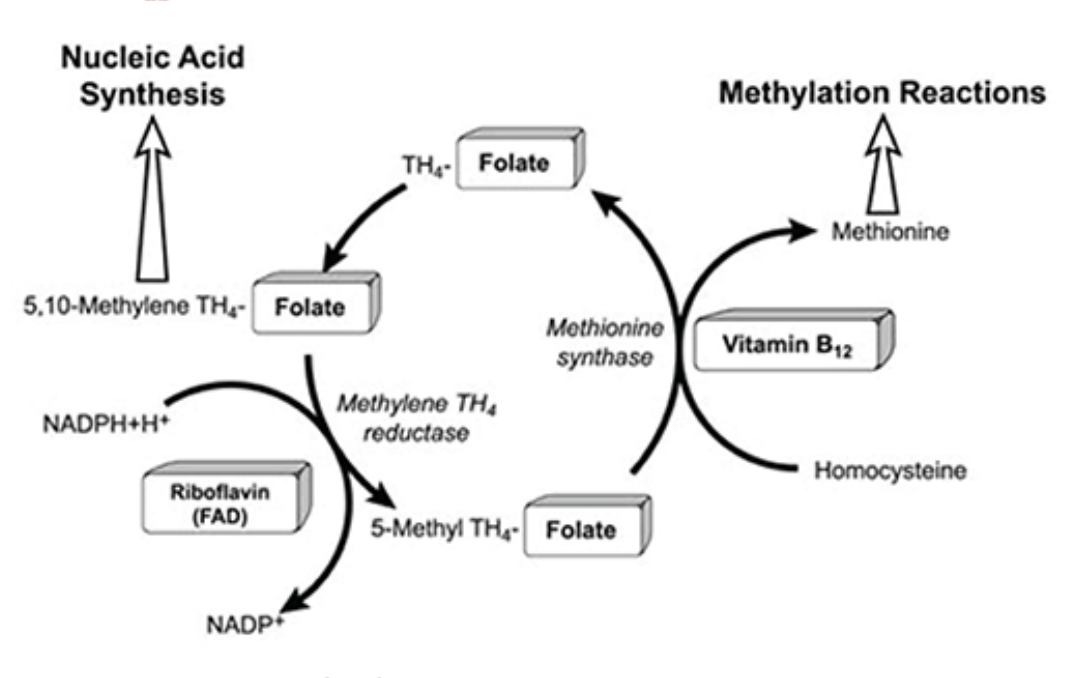
Symptoms of vitamin B_{12} deficiency

Vitamin B_{12} deficiency results in impairment of the activities of vitamin B_{12}-requiring enzymes. Impaired activity of methionine synthase results in elevated homocysteine levels, while impaired activity of L-methylmalonyl-CoA mutase results in increased levels of a metabolite of methylmalonyl-CoA called methylmalonic acid (MMA). While individuals with mild vitamin B_{12} deficiency may not experience symptoms, blood levels of homocysteine and/or MMA may be elevated (15).

Megaloblastic anemia

Diminished activity of methionine synthase in vitamin B_{12} deficiency inhibits the regeneration of tetrahydrofolate (THF) and traps folate in a form that is not usable by the body (**Figure 3**), resulting in symptoms of folate deficiency even in the presence of adequate folate levels. Thus, in both folate and vitamin B_{12} deficiencies, folate is unavailable to participate in DNA synthesis. This impairment of DNA synthesis affects the rapidly dividing cells of the bone marrow earlier than other cells, resulting in the production of large, immature, hemoglobin-poor red blood cells. The resulting anemia is known as megaloblastic anemia and is the symptom for which the disease, pernicious anemia, was named (3). Supplementation with folic acid will provide enough usable folate to restore normal red blood cell formation. However, if vitamin B_{12} deficiency is the cause, it will persist despite the resolution of the anemia. Thus, megaloblastic anemia should not be treated with folic acid until the underlying cause has been determined (16).

Figure 3. Vitamin B_{12} and Nucleic Acid Metabolism



5,10-Methylene tetrahydrofolate (TH_4) is required for the synthesis of nucleic acids, while 5-methyl TH_4 is required for the formation of methionine from homocysteine. Methionine, in the form of S-adenosylmethionine, is required for many biological methylation reactions, including DNA methylation. Methylene TH_4 reductase is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methylene TH_4 to 5-methyl TH_4.

Neurologic symptoms

The neurologic symptoms of vitamin B_{12} deficiency include numbness and tingling of the hands and, more commonly, the feet; difficulty walking; memory loss; disorientation; and dementia with or without mood changes. Although the progression of neurologic complications is generally gradual, such symptoms may not be reversed with treatment of vitamin B_{12} deficiency, especially if they have been present for a long time. Neurologic complications are not always associated with megaloblastic anemia and are the only clinical symptom of vitamin B_{12} deficiency in about 25% of cases (17). Although vitamin B_{12} deficiency is known to damage the myelin sheath covering cranial, spinal, and peripheral nerves, the biochemical processes leading to neurological damage in vitamin B_{12} deficiency are not yet fully understood (18).

Gastrointestinal symptoms

Tongue soreness, appetite loss, and constipation have also been associated with vitamin B_{12} deficiency. The origins of these symptoms are unclear, but they may be related to the stomach inflammation underlying some cases of vitamin B_{12} deficiency and to the progressive destruction of the lining of the stomach (17).

The Recommended Dietary Allowance (RDA)

The RDA for vitamin B_{12} was revised by the Food and Nutrition Board (FNB) of the US Institute of Medicine in 1998 (**Table 1**). Because of the increased risk of food-bound vitamin B_{12} malabsorption in older adults, the FNB recommended that adults over 50 years of age get most of the RDA from fortified food or vitamin B_{12}-containing supplements (17).

Table 1. Recommended Dietary Allowance (RDA) for Vitamin B_{12}

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	0.4 (AI)	0.4 (AI)
Infants	7-12 months	0.5 (AI)	0.5 (AI)
Children	1-3 years	0.9	0.9
Children	4-8 years	1.2	1.2
Children	9-13 years	1.8	1.8
Adolescents	14-18 years	2.4	2.4
Adults	19-50 years	2.4	2.4
Adults	51 years and older	2.4*	2.4*
Pregnancy	all ages	-	2.6
Breast-feeding	all ages	-	2.8

*Vitamin B_{12} intake should be from supplements or fortified foods due to the age-related increase in food-bound malabsorption.

Disease Prevention

Cardiovascular disease

As mentioned above, chronic atrophic gastritis and infection by *H. pylori* can cause deficiency in vitamin B_{12} secondary to malabsorption disorders (see Causes of vitamin B_{12} deficiency). However, the occurrence of *H. pylori* infection and chronic atrophic gastritis did not modify the five-year incidence of cardiovascular accidents (stroke and heart attack) or mortality in a large cohort study of nearly 10,000 men and women over 50 years old (19). Yet, vitamin B_{12} status was not assessed in this study, despite the high prevalence of vitamin B_{12} deficiency in older individuals.

Homocysteine and cardiovascular disease

Epidemiological studies indicate that even moderately elevated levels of homocysteine in the blood raise the risk of cardiovascular disease (CVD) (20), though the mechanism by which homocysteine may increase the CVD risk remains the subject of a great deal of research (21). The amount of homocysteine in the blood is regulated by at least three vitamins: folate, vitamin B_6, and vitamin B_{12} (see **Figure 1** above). An early analysis of the results of 12 randomized controlled trials showed that folic acid supplementation (0.5-5 mg/day) had the greatest lowering effect on blood homocysteine levels (25% decrease); co-supplementation with folic acid and vitamin B_{12} (500 μg/day) provided an additional 7% reduction (32% decrease) in blood homocysteine concentrations (22). The results of a sequential supplementation trial in 53 men and women indicated that after folic acid supplementation, vitamin B_{12} became the major determinant of plasma homocysteine levels (23). It is thought that the elevation of homocysteine levels might be partly due to vitamin B_{12} deficiency in individuals over 60 years of age. Two studies found blood methylmalonic acid (MMA) levels to be elevated in more than 60% of elderly individuals with elevated homocysteine levels. In the absence of impaired kidney function, an elevated MMA level in conjunction with elevated homocysteine suggests either a vitamin B_{12} deficiency or a combined vitamin B_{12} and folate deficiency (24). Thus, it appears important to evaluate vitamin B_{12} status, as well as kidney function, in older individuals with elevated homocysteine levels prior to initiating homocysteine-lowering therapy. For more information regarding homocysteine and CVD, see the article on Folate.

Intervention studies

Although increased intake of folic acid and vitamin B_{12} is effective in decreasing homocysteine levels, the combined intervention of these B vitamins did not lower risk for CVD. Indeed, several randomized, placebo-controlled trials have been conducted to determine whether homocysteine-lowering through folic acid, vitamin B_{12}, and vitamin B_6 supplementation reduces the incidence of CVD. A recent meta-analysis of data from 11 trials, including nearly 45,000 participants at risk of CVD, showed that B-vitamin supplementation had no significant effect on risk of myocardial infarction (heart attack) or stroke, nor did it modify the risk of all-cause mortality (25). Other meta-analyses that included patients with chronic kidney disease have confirmed the lack of effect of homocysteine-lowering on risk of myocardial infarction and death. However, stroke risk was significantly reduced by 7%-12% with the B-vitamin supplementation (26, 27). Another meta-analysis of 12 clinical trials measuring flow-mediated vasodilation (FMD; a surrogate marker of vascular health) in response to homocysteine reduction revealed that B-vitamin supplementation was accompanied by an improved FMD in short-term <8 weeks) but not in long-term studies conducted in subjects with preexisting vascular diseases (28). Yet, some of the studies included in these meta-analyses did not use vitamin B_{12}, and folate administration on its own has shown a protective role on vascular function and stroke risk (29). Besides, the high prevalence of malabsorption disorders and vitamin B_{12} deficiency in elderly individuals might warrant the use of higher doses of vitamin B_{12} than those used in these trials (30); in cases of malabsorption, only high-dose oral therapy or intramuscular injections can overcome vitamin B_{12} deficiency (4).

Cancer

Folate is required for synthesis of DNA, and there is evidence that decreased availability of folate results in strands of DNA that are more susceptible to damage. Deficiency of vitamin B_{12} traps folate in a form that is unusable by the body for DNA synthesis. Both vitamin B_{12} and folate deficiencies result in a diminished capacity for methylation reactions (see **Figure 3** above). Thus, vitamin B_{12} deficiency may lead to an elevated rate of DNA damage and altered methylation of DNA, both of which are important risk factors for cancer. A series of studies in young adults and older men indicated that increased levels of homocysteine and decreased levels of vitamin B_{12} in the blood were associated with a biomarker of chromosome breakage in white blood cells (reviewed in 31). In a double-blind, placebo-controlled study, the same biomarker of chromosome breakage was minimized in young adults who were supplemented with 700 μg of folic acid and 7 μg of vitamin B_{12} daily in cereal for two months (32).

Breast cancer

A case-control study compared prediagnostic levels of serum folate, vitamin B_6, and vitamin B_{12} in 195 women later diagnosed with breast cancer and 195 age-matched, cancer-free women. Among postmenopausal women, the association between blood levels of vitamin B_{12} and breast cancer suggested a threshold effect. The risk of breast cancer was more than doubled in women with serum vitamin B_{12} levels in the lowest quintile compared to women in the four highest quintiles (33). However, the meta-analysis of this study with three additional case-control studies found no protection associated with high compared to low vitamin B_{12} serum levels (34). A case-control study in Mexican women (475 cases and 1,391 controls) reported that breast cancer risk for women in the highest quartile of vitamin B_{12} intake (7.3-7.7 μg/day) was 68% lower than those in the lowest quartile (2.6 μg/day). Stratification of the data revealed that the inverse association between dietary vitamin B_{12} intake and breast cancer risk was stronger in postmenopausal women compared to premenopausal women, though both associations were statistically significant. Moreover, among postmenopausal women, the apparent protection conferred by folate was only observed in women with the highest vitamin B_{12} quartiles of intake (35). However, more recent case-control and prospective cohort studies have reported weak to no risk reduction with vitamin B_{12} intakes in different populations, including Hispanic, African American and European American women (36, 37). A meta-analysis of seven case-control and seven prospective cohort studies concluded that the risk of breast cancer was not modified by high versus low vitamin B_{12} intakes (34). There was no joint association between folate and vitamin B_{12} intakes and breast cancer risk. Presently, there is little evidence to suggest a relationship between vitamin B_{12} status and breast cancer. In addition, results from observational studies are not consistently in support of an association between high dietary folate intakes and reduced risk for breast cancer (see the article on Folate). There is a need to evaluate the effect of folate and vitamin B_{12} supplementation in well-controlled, randomized, clinical trials, while considering various factors that modify breast cancer risk, such as menopausal status, ethnicity, and alcohol intake.

Neural tube defects

Neural tube defects (NTD) may result in anencephaly or spina bifida, which are mostly fatal congenital malformations of the central nervous system. The defects arise from failure of embryonic neural tube to close, which occurs between the 21st and 28th days after conception, a time when many women are unaware of their pregnancy (38). Randomized controlled trials have demonstrated 60% to 100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the month before and the month after conception. Increasing evidence indicates that the homocysteine-lowering effect of folic acid plays a critical role in reducing the risk of NTD (39). Homocysteine may accumulate in the blood when there is inadequate folate and/or vitamin B_{12} for effective functioning of the methionine synthase enzyme. Decreased vitamin B_{12} levels and elevated homocysteine concentrations have been found in the blood and amniotic fluid of pregnant women at high risk of NTD (40). The recent meta-analysis of 12 case-control studies, including 567 mothers with current or prior NTD-affected pregnancy and 1,566 unaffected mothers, showed that low maternal vitamin B_{12} status was associated with an increased risk of NTD (41). Yet, whether vitamin B_{12} supplementation may be beneficial in the prevention of NTD has not been evaluated (42).

Cognitive decline, dementia, and Alzheimer's disease

The occurrence of vitamin B_{12} deficiency prevails in the elderly population and has been frequently associated with Alzheimer's disease (reviewed in 43). One study found lower vitamin B_{12} levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia, though blood levels of vitamin B_{12} did not differ (44). The reason for the association of low vitamin B_{12} status with Alzheimer's disease is not clear. Vitamin B_{12} deficiency, like folate deficiency, may lead to decreased synthesis of methionine and S-adenosylmethionine (SAM), thereby adversely affecting methylation reactions. Methylation reactions are essential for the metabolism of components of the myelin sheath of nerve cells as well as for synthesis of neurotransmitters (18). Other metabolic implications of vitamin B_{12} deficiency include the accumulation of homocysteine and methylmalonic acid, which might contribute to the neuropathologic features of dementia (43).

Observational studies

A large majority of cross-sectional and prospective cohort studies have associated elevated homocysteine concentrations with measures of poor cognitive scores and increased risk of dementia, including Alzheimer's disease (reviewed in 45). A case-control study of 164 patients with dementia of Alzheimer's type included 76 cases in which the diagnosis of Alzheimer's disease was confirmed by examination of brain cells after death. Compared to 108 control subjects without evidence of dementia, subjects with dementia of Alzheimer's type and confirmed Alzheimer's disease had higher blood homocysteine levels and lower blood levels of folate and vitamin B_{12}. Measures of general nutritional status indicated that the association of increased homocysteine levels and diminished vitamin B_{12} status with Alzheimer's disease was not due to dementia-related malnutrition (46). In a sample of 1,092 men and women without dementia followed for an average of 10 years, those with higher plasma homocysteine levels at baseline had a significantly higher risk of developing Alzheimer's disease and other types of dementia. Specifically, those with plasma homocysteine levels greater than 14 μmol/L had nearly double the risk of developing Alzheimer's disease (47). A study in 650 elderly men and women reported that the risk of elevated plasma homocysteine levels was significantly higher in those with lower cognitive function scores (48). A prospective study in 816 elderly men and women reported that those with hyperhomocysteinemia (homocysteine levels >15 μmol/L) had a significantly higher risk of developing Alzheimer's disease or dementia. Although raised homocysteine levels might be partly due to a poor vitamin B_{12} status, the latter was not related to risk of Alzheimer's disease or dementia in this study (49).

A recent systematic review of 35 prospective cohort studies assessing the association between vitamin B_{12} status and cognitive deterioration in older individuals with or without dementia at baseline did not support a relationship between vitamin B_{12} serum concentrations and cognitive decline, dementia, or Alzheimer's disease (50). Nevertheless, studies utilizing more sensitive biomarkers of vitamin B_{12} status, including measures of holo-transcobalamin (holo-TC; a vitamin B_{12} carrier) and methylmalonic acid, showed more consistent results and a trend toward associations between poor vitamin B_{12} status and faster cognitive decline and risk of Alzheimer's disease (51-55). Besides, it cannot be excluded that the co-occurrence of potential confounders like elevated homocysteine level and poor folate status might mitigate the true contribution of vitamin B_{12} status to cognitive functioning (45).

Intervention studies

High-dose B-vitamin supplementation has been proven effective for treating hyperhomocysteinemia in elderly individuals with or without cognitive impairment. However, homocysteine-lowering trials have produced equivocal results regarding the prevention of cognitive deterioration in this population. A systematic review and meta-analysis of 18 randomized, placebo-controlled trials examining the effect of B-vitamin supplementation did not find that the decrease in homocysteine level prevented or delayed cognitive decline among older subjects (56). A more recent randomized, double-blind, placebo-controlled clinical trial in 900 older individuals at high risk of cognitive impairment found that daily supplementation of 400 μg of folic acid and 100 μg of vitamin B_{12} for two years significantly improved measures of immediate and delayed memory and slowed the rise in plasma homocysteine concentrations (57). However, supplemented subjects had no reduction in homocysteine concentrations compared to baseline, nor did they perform better in processing speed tests compared to placebo. Another two-year, randomized, placebo-controlled study in elderly adults reported that a daily regimen of 800 μg of folic acid, 500 μg of vitamin B_{12}, and 20 mg of vitamin B_6 significantly reduced the rate of brain atrophy compared to placebo treatment (0.5% vs. 3.7%). Interestingly, a greater benefit was seen in those with high compared to low homocysteine concentrations at baseline, suggesting the importance of lowering homocysteine levels in prevention of brain atrophy and cognitive decline (58, 59). The authors attributed the changes in homocysteine levels primarily to vitamin B_{12} (59). Finally, the most recent randomized, double blind, placebo-controlled trial in over 2,500 individuals who suffered a stroke showed that the normalization of homocysteine concentrations by B-vitamin supplementation (2 mg of folic acid, 500 μg of vitamin B_{12}, and 25 mg of vitamin B_6) did not improve cognitive performance or decrease incidence of cognitive decline compared to placebo (60). Currently, there is a need for larger trials to evaluate the effect of B-vitamin supplementation on long-term outcomes, such as the incidence of Alzheimer's disease.

Depression

Observational studies have found as many as 30% of patients hospitalized for depression are deficient in vitamin B_{12} (61). A cross-sectional study of 700 community-living, physically disabled women over the age of 65 found that vitamin B_{12}-deficient women were twice as likely to be severely depressed as non-deficient women (62). A population-based study in 3,884 elderly men and women with depressive disorders found that those with vitamin B_{12} deficiency were almost 70% more likely to experience depression than those with normal vitamin B_{12} status (63). The reasons for the relationship between vitamin B_{12} deficiency and depression are not clear but may involve a shortage in S-adenosylmethionine (SAM). SAM is a methyl group donor for numerous methylation reactions in the brain, including those involved in the metabolism of neurotransmitters whose deficiency has been related to depression (64). Severe vitamin B_{12} deficiency in a mouse model showed dramatic alterations in the level of DNA methylation in the brain, which might lead to neurologic impairments (65). This hypothesis is supported by several studies that have shown supplementation with SAM improves depressive symptoms (66-69).

Increased homocysteine level is another nonspecific biomarker of vitamin B_{12} deficiency that has been linked to depressive symptoms in the elderly (70). However, in a recent cross-sectional study conducted in 1,677 older individuals, higher vitamin B_{12} plasma levels, but not changes in homocysteine concentrations, were correlated with a lower prevalence of depressive symptoms (71). Few studies have examined the relationship of vitamin B_{12} status, homocysteine levels, and the development of depression over time. In a randomized, placebo-controlled, intervention study with over 900 older participants experiencing psychological distress, daily supplementation with folic acid (400 μg) and vitamin B_{12} (100 μg) for two years did not reduce the occurrence of symptoms of depression despite significantly improving blood folate, vitamin B_{12}, and homocysteine levels compared to placebo (72). However, in a long-term randomized, double-blind, placebo-controlled study among sufferers of cerebrovascular accidents at high risk of depression, daily supplementation with 2 mg of folic acid, 25 mg of vitamin B_6, and 500 μg vitamin B_{12} significantly lowered the risk of major depressive episodes during a seven-year follow-up period compared to placebo (73). Although it cannot yet be determined whether vitamin B_{12} deficiency plays a causal role in depression, it may be beneficial to screen for vitamin B_{12} deficiency in older individuals as part of a medical evaluation for depression.

Osteoporosis

High homocysteine levels may affect bone remodeling by increasing bone resorption (breakdown), decreasing bone formation, and reducing bone blood flow. Another proposed mechanism involves the binding of homocysteine to the collagenous matrix of bone, which may modify collagen properties and reduce bone strength (reviewed in 74). Alterations of bone biomechanical properties can contribute to osteoporosis and increase the risk of fractures in the elderly. Since vitamin B_{12} is a determinant of homocysteine metabolism, it was suggested that the risk of osteoporotic fractures in older subjects might be enhanced by vitamin B_{12} deficiency. A meta-analysis of four observational studies, following a total of 7,475 older individuals for 3 to 16 years, found a weak association between an elevation in vitamin B_{12} of 50 picomoles/L in blood and a reduction in fracture risk (75). A randomized, placebo-controlled trial in 559 elderly individuals with low serum levels of folate and vitamin B_{12} and at increased risk of fracture evaluated the combined supplementation of very high doses of folic acid (5 mg/day) and vitamin B_{12} (1.5 mg/day). The two-year study found that the supplementation improved B-vitamin status, decreased homocysteine concentrations, and reduced risk of total fractures compared to placebo (76). However, a multicenter study in 5,485 subjects with cardiovascular disease or diabetes mellitus showed that daily supplementation with folic acid (2.5 mg), vitamin B_{12} (1 mg), and vitamin B_6 (50 mg) lowered homocysteine concentrations but had no effect on fracture risk compared to placebo (77). Another small, randomized, double-blind trial in 93 individuals with low vitamin D status found no additional benefit of B-vitamin supplementation (50 mg/day of vitamin B_6, 0.5 mg/day of folic acid, and 0.5 mg/day of vitamin B_{12}) on markers of bone health over a one-year period beyond that associated with vitamin D and calcium supplementation. Yet, the short length of the study did not permit a conclusion on whether the lowering of homocysteine through B-vitamin supplementation could have long-term benefits on bone strength and fracture risk (78). A large intervention study conducted in older people with no preexisting conditions is under way to evaluate the effect of B-vitamin supplementation on markers of bone health and incidence of fracture; this trial might clarify whether B vitamins could have a protective effect on bone health in the elderly population (79).

Sources

Food sources

Only bacteria can synthesize vitamin B_{12} (80). Vitamin B_{12} is present in animal products, such as meat, poultry, fish (including shellfish), and to a lesser extent dairy products and eggs (1). Fresh pasteurized milk contains 0.9 μg per cup and is an important source of vitamin B_{12} for some vegetarians (17). Those strict vegetarians who eat no animal products (vegans) need supplemental vitamin B_{12} to meet their requirements. Recent analyses revealed that some plant-source foods, such as certain fermented beans and vegetables and edible algae and mushrooms, contain substantial amounts of bioactive vitamin B_{12} (81). Together with B-vitamin fortified food and supplements, these foods may contribute, though modestly, to prevent vitamin B_{12} deficiency in individuals consuming vegetarian diets. Also, individuals over the age of 50 should obtain their vitamin B_{12} in supplements or fortified foods (e.g., fortified cereals) because of the increased likelihood of food-bound vitamin B_{12} malabsorption with increasing age.

Most people do not have a problem obtaining the RDA of 2.4 μg/day of vitamin B_{12} in food. According to a US national survey, the average dietary intake of vitamin B_{12} is 5.4 μg/day for adult men and 3.4 μg/day for adult women. Adults over the age of 60 had an average dietary intake of 4.8 μg/day (42). However, consumption of any type of vegetarian diet dramatically increases the prevalence of vitamin B_{12} deficiency in individuals across all age groups (82). Some foods with substantial amounts of vitamin B_{12} are listed in **Table 2**, along with their vitamin B_{12} content in micrograms (μg). For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin B_{12}

Food	Serving	Vitamin B_{12} (μg)
Clams (steamed)	3 ounces	84.1
Mussels (steamed)	3 ounces	20.4
Mackerel (Atlantic, cooked, dry-heat)	3 ounces*	16.1
Crab (Alaska king, steamed)	3 ounces	9.8
Beef (lean, plate steak, cooked, grilled)	3 ounces	6.9
Salmon (chinook, cooked, dry-heat)	3 ounces	2.4
Rockfish (cooked, dry-heat)	3 ounces	1.0
Milk (skim)	8 ounces	0.9
Turkey (cooked, roasted)	3 ounces	0.8
Brie (cheese)	1 ounce	0.5
Egg (poached)	1 large	0.4
Chicken (light meat, cooked, roasted)	3 ounces	0.3

*A three-ounce serving of meat or fish is about the size of a deck of cards.

Supplements

Cyanocobalamin is the principal form of vitamin B_{12} used in oral supplements, but methylcobalamin is also available as a supplement. Cyanocobalamin is available by prescription in an injectable form and as a nasal gel for the treatment of pernicious anemia. Over-the-counter preparations containing cyanocobalamin include multivitamins, vitamin B-complex supplements, and single-nutrient, vitamin B_{12} supplements (83).

Safety

Toxicity

No toxic or adverse effects have been associated with large intakes of vitamin B_{12} from food or supplements in healthy people. Doses as high as 2 mg (2,000 μg) daily by mouth or 1 mg monthly by intramuscular (IM) injection have been used to treat pernicious anemia without significant side effects (84). When high doses of vitamin B_{12} are given orally, only a small percentage can be absorbed, which may explain the low toxicity (4). Because of the low toxicity of vitamin B_{12}, no tolerable upper intake level (UL) has been set by the US Food and Nutrition Board (17).

Drug interactions

A number of drugs reduce the absorption of vitamin B_{12}. Proton-pump inhibitors (e.g., omeprazole and lansoprazole), used for therapy of Zollinger-Ellison syndrome and gastroesophageal reflux disease (GERD), markedly decrease stomach acid secretion required for the release of vitamin B_{12} from food but not from supplements. Long-term use of proton-pump inhibitors has been found to decrease blood vitamin B_{12} levels. However, vitamin B_{12} deficiency does not generally develop until after at least three years of continuous therapy (85, 86). Another class of gastric acid inhibitors known as histamine$_2$ (H_2)-receptor antagonists (e.g., cimetidine, famotidine, and ranitidine), often used to treat peptic ulcer disease, has also been found to decrease the absorption of vitamin B_{12} from food. It is not clear whether the long-term use of H_2-receptor antagonists could cause overt vitamin B_{12} deficiency (87, 88). Individuals taking drugs that inhibit gastric acid secretion should consider taking vitamin B_{12} in the form of a supplement because gastric acid is not required for its absorption. Other drugs found to inhibit vitamin B_{12} absorption from food include cholestyramine (a bile acid-binding resin used in the treatment of high cholesterol), chloramphenicol and neomycin (antibiotics), and colchicine (medicine for gout treatment). Metformin, a medication for individuals with type 2 diabetes, was found to decrease vitamin B_{12} absorption by tying up free calcium required for absorption of the IF-B_{12} complex (89). However, the clinical significance of this is unclear (90). It is not known whether calcium supplementation can reverse vitamin B_{12} malabsorption; therefore, calcium supplementation is not currently prescribed for the prevention or treatment of metformin-induced vitamin B_{12} deficiency (91). Previous reports that megadoses of vitamin C destroy vitamin B_{12} have not been supported (92) and may have been an artifact of the assay used to measure vitamin B_{12} levels (17).

Nitrous oxide, a commonly used anesthetic, oxidizes and inactivates vitamin B_{12}, thus inhibiting both of the vitamin B_{12}-dependent enzymes, and can produce many of the clinical features of vitamin B_{12} deficiency, such as megaloblastic anemia or neuropathy. Since nitrous oxide is commonly used for surgery in the elderly, some experts feel vitamin B_{12} deficiency should be ruled out prior to its use (6, 15).

Large doses of folic acid given to an individual with an undiagnosed vitamin B_{12} deficiency could correct megaloblastic anemia without correcting the underlying vitamin B_{12} deficiency, leaving the individual at risk of developing irreversible neurologic damage (17). For this reason, the Food and Nutrition Board of the US Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 µg (1 mg) daily.

Linus Pauling Institute Recommendation

A varied diet should provide enough vitamin B_{12} to prevent deficiency in most individuals 50 years of age and younger. Strict vegetarians and women planning to become pregnant should take a multivitamin supplement daily or eat fortified cereal, which would ensure a daily intake of 6 to 30 µg of vitamin B_{12} in a form that is easily absorbed. Higher doses of vitamin B_{12} supplements are recommended for patients taking medications that interfere with its absorption (see Drug interactions).

Older adults (>50 years)

Because vitamin B_{12} malabsorption and vitamin B_{12} deficiency are more common in older adults, the Linus Pauling Institute recommends that adults older than 50 years take 100 to 400 µg/day of supplemental vitamin B_{12}.

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Vitamin C

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Español

Summary

- Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin. Unlike most mammals and other animals, humans do not have the ability to synthesize vitamin C and must obtain it from the diet. *(More information)*
- Vitamin C is an essential cofactor in numerous enzymatic reactions, e.g., in the biosynthesis of collagen, carnitine, and neuropeptides, and in the regulation of gene expression. It is also a potent antioxidant. *(More information)*
- Prospective cohort studies indicate that higher vitamin C status, assessed by measuring circulating vitamin C, is associated with lower risks of hypertension, coronary heart disease, and stroke. *(More information)*
- There is some evidence to suggest that vitamin C may be a useful adjunct to conventional medical practice to reduce myocardial injury and arrhythmia following a cardiac procedure or surgery in patients with cardiovascular disease. *(More information)*
- There are insufficient data to suggest a link between vitamin C status and the risk of developing a given type of cancer. Most observational studies examining vitamin C intake in relation to cancer incidence have found no association. Randomized controlled trials have reported no effect of vitamin C supplementation on cancer risk. *(More information)*
- Current evidence of the efficacy of intravenous vitamin C in cancer patients is limited to observational studies, uncontrolled interventions, and case reports. There is a need for large, longer-duration phase II clinical trials that test the efficacy of intravenous vitamin C in cancer progression and overall survival. *(More information)*
- Overall, regular use of vitamin C supplements shortens the duration of the common cold but does not reduce the risk of becoming ill. Taking supplements once cold symptoms have already begun has no proven benefits. *(More information)*
- Vitamin C supplements are available in many forms, but there is little scientific evidence that any one form is better absorbed or more effective than another. *(More information)*
- There is no scientific evidence that large amounts of vitamin C (up to 10 grams [g]/day in adults) exert any adverse or toxic effects. An upper intake level of 2 g/day is recommended in order to prevent some adults from experiencing diarrhea and gastrointestinal disturbances. *(More information)*
- Supplemental vitamin C increases urinary oxalate concentrations, but whether an increase in urinary oxalate elevates the risk for kidney stones is not yet known. Those predisposed for kidney stone formation may consider avoiding high-dose (≥1 g/day) vitamin C supplementation. *(More information)*

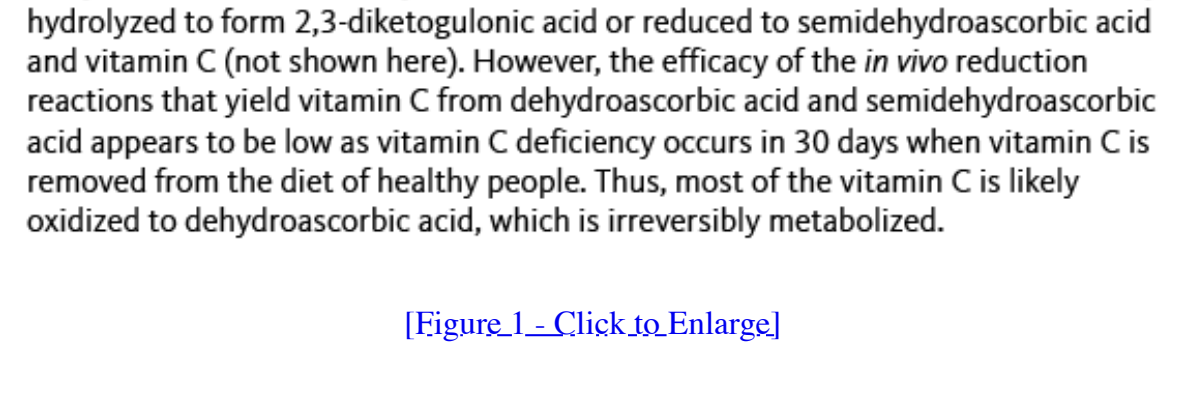
Function

Vitamin C (L-ascorbic acid) is a potent reducing agent, meaning that it readily donates electrons to recipient molecules (**Figure 1**). Related to this oxidation-reduction (redox) potential, two major functions of vitamin C are as an antioxidant and as an enzyme cofactor (1).

Vitamin C is the primary water-soluble, non-enzymatic antioxidant in plasma and tissues. Even in small amounts, vitamin C can protect indispensable molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA), from damage by free radicals and reactive oxygen species (ROS) that are generated during normal metabolism, by active immune cells, and through exposure to toxins and pollutants (e.g., certain chemotherapy drugs and cigarette smoke). Vitamin C also participates in redox recycling of other important antioxidants; for example, vitamin C is known to regenerate vitamin E from its oxidized form (see the article on Vitamin E).

The role of vitamin C as a cofactor is also related to its redox potential. By maintaining enzyme-bound metals in their reduced forms, vitamin C assists mixed-function oxidases in the synthesis of several critical biomolecules (1). These enzymes are either monooxygenases or dioxygenases (see **Table 1**). Symptoms of vitamin C deficiency, such as poor wound healing and lethargy, likely result from the impairment of these vitamin C-dependent enzymatic reactions leading to the insufficient synthesis of collagen, carnitine, and catecholamines (see Deficiency). Moreover, several dioxygenases involved in the regulation of gene expression and the maintenance of genome integrity require vitamin C as a cofactor. Indeed, research has recently uncovered the crucial role played by enzymes, such as the TET dioxygenases and Jumonji domain-containing histone demethylases, in the fate of cells and tissues (see **Table 1**). These enzymes contribute to the epigenetic regulation of gene expression by catalyzing reactions involved in the demethylation of DNA and histones.

Figure 1. Vitamin C



Vitamin C (L-ascorbic acid) is an electron donor. Vitamin C can sequentially donate two electrons. Vitamin C can donate electrons to reactive free radicals, which then become reduced. The loss of one electron results in vitamin C being oxidized to the ascorbate free radical, which is relatively unreactive compared to other free radicals. The ascorbate free radical can be reduced to vitamin C by gaining one electron or be further oxidized to dehydroascorbic acid by losing another electron. Dehydroascorbic acid is only stable for a few minutes and is then either irreversibly hydrolyzed to form 2,3-diketogulonic acid or reduced to semidehydroascorbic acid and vitamin C (not shown here). However, the efficacy of the *in vivo* reduction reactions that yield vitamin C from dehydroascorbic acid and semidehydroascorbic acid appears to be low as vitamin C deficiency occurs in 30 days when vitamin C is removed from the diet of healthy people. Thus, most of the vitamin C is likely oxidized to dehydroascorbic acid, which is irreversibly metabolized.

[Figure 1 - Click to Enlarge]

Table 1. Enzymes Requiring Vitamin C as a Cofactor in Mammals (1, 2)

Enzymes*	Functions
Monooxygenases	
Dopamine β-monooxygenase	Norepinephrine (Noradrenaline) biosynthesis
Peptidyl-glycine α-amidating monooxygenase	Amidation of peptide hormones
Dioxygenases	
3 Prolyl 4-hydroxylase isoenzymes	Collagen hydroxylation
3 Prolyl 3-hydroxylase isoenzymes	Collagen hydroxylation
3 Lysyl hydroxylase isoenzymes	Collagen hydroxylation
4 Hypoxia-inducible factor (HIF) isoenzymes	HIF hydroxylation
Trimethyllysine hydroxylase	Carnitine biosynthesis
γ-Butyrobetaine hydroxylase	Carnitine biosynthesis
4-Hydroxyphenylpyruvate dioxygenase	Tyrosine metabolism
Ten-eleven translocation (TET) family of dioxygenases	Demethylation of DNA
Jumonji domain-containing histone demethylases	Demethylation of histones
*Monooxygenases catalyze the hydroxylation of one substrate, whereas dioxygenases catalyze a reaction that couples the hydroxylation of a specific substrate with the conversion (decarboxylation) of α-ketoglutarate into succinate.	

The capacity of vitamin C to influence the methylation status of DNA and histones in mammalian cells supports a role for the vitamin in health and disease beyond what was previously understood, in particular by safeguarding genome integrity (3, 4).

Role in immunity

Vitamin C affects several components of the human immune system *in vitro*; for example, vitamin C has been shown to stimulate both the production (5-9) and function (10, 11) of leukocytes (white blood cells), especially neutrophils, lymphocytes, and phagocytes. Specific measures of functions stimulated by vitamin C include cellular motility (10), chemotaxis (10, 11), and phagocytosis (11). Neutrophils, mononuclear phagocytes, and lymphocytes accumulate vitamin C to high concentrations, which can protect these cell types from oxidative damage (12-14). In response to invading microorganisms, phagocytic leukocytes release non-specific toxins, such as superoxide radicals, hypochlorous acid ("bleach"), and peroxynitrite; these reactive oxygen species kill pathogens and, in the process, can damage the leukocytes themselves (15). Vitamin C, through its antioxidant functions, has been shown to protect leukocytes from self-inflicted oxidative damage (14). Phagocytic leukocytes also produce and release cytokines, including interferons, which have antiviral activity (16). Vitamin C has been shown to increase interferon production *in vitro* (17). Additional studies have reported that vitamin C enhances the chemotactic and microbial killing capacities of neutrophils and stimulates the proliferation and differentiation of B- and T-lymphocytes (reviewed in 18).

It is widely thought by the general public that vitamin C boosts immune function, yet human studies published to date are conflicting. Disparate results are likely due to study design issues, often linked to a lack of understanding of vitamin C pharmacokinetics and requirements (19, 20).

Finally, vitamin C increases the bioavailability of iron from foods by enhancing intestinal absorption of non-heme iron (see the article on Iron) (21).

Bioavailability

Depletion-repletion pharmacokinetic experiments demonstrated that plasma vitamin C concentration is tightly controlled by three primary mechanisms: intestinal absorption, tissue transport, and renal reabsorption (22). In response to increasing oral doses of vitamin C, plasma vitamin C concentration rises steeply at intakes between 30 and 100 mg/day. Plasma concentrations of ascorbate reach steady-state at concentrations between 60 and 80 micromoles/L (µmol/L). This is typically observed at doses between 200 to 400 mg/day in healthy young adults, with some degree of individual variation (23, 24).

One hundred percent absorption efficiency is observed when ingesting vitamin C at doses up to 200 mg at a time. Higher doses (>500 mg) result in fractionally less vitamin C being absorbed as the dose increases. Once plasma vitamin C concentrations reach saturation, additional vitamin C is largely excreted in the urine. Notably, intravenous administration of vitamin C bypasses absorptive control in the intestine such that very high concentrations of vitamin C can be achieved in the plasma; within a few hours, renal excretion restores vitamin C to baseline plasma concentrations (see Cancer Treatment) (25).

While plasma vitamin C concentration reflects recent dietary intake, leukocyte (white blood cell) vitamin C is thought to be an indicator of body stores. However, leukocyte vitamin C concentration does not accurately reflect vitamin C in several tissues and may specifically underestimate vitamin C uptake into skeletal muscle (26). Yet, plasma concentrations of vitamin C ≥50 µmol/L are sufficient to saturate muscle tissue vitamin C.

There is also some limited evidence suggesting that individuals who carry certain polymorphisms in genes involved in vitamin C transport and detoxification mechanisms may have lower plasma vitamin C concentrations even with high vitamin C intakes (see also Vascular complications of diabetes mellitus) (reviewed in 27).

Due to the pharmacokinetics and tight regulation of plasma vitamin C, supplementation with vitamin C will have variable effects in vitamin C-replete (plasma concentrations near saturation) versus sub-optimal (plasma concentrations <50 µmol/L), marginally deficient (plasma concentrations <23 µmol/L), or severely deficient (plasma concentrations <11 µmol/L) individuals (28). Scientific studies investigating vitamin C efficacy to prevent or treat disease need to assess baseline vitamin C status before embarking on an intervention or statistical analysis (22, 29-31).

For a more detailed discussion on the bioavailability of different forms of vitamin C, see the article, The Bioavailability of Different Forms of Vitamin C.

Deficiency

Severe vitamin C deficiency has been known for many centuries as the potentially fatal disease, scurvy. By the late 1700s, the British navy was aware that scurvy could be cured by eating oranges or lemons, even though vitamin C would not be isolated until the early 1930s. Symptoms of scurvy include subcutaneous bleeding, poor wound closure, and bruising easily, hair and tooth loss, and joint pain and swelling. Such symptoms appear to be related to the weakening of blood vessels, connective tissue, and bone, which all contain collagen. Early symptoms of scurvy like fatigue may result from diminished levels of carnitine, which is needed to derive energy from fat, or from decreased synthesis of the catecholamine norepinephrine (see Function). Scurvy is rare in developed countries because it can be prevented by as little as 10 mg of vitamin C daily (32). However, cases have occurred in children and the elderly on very restricted diets (33, 34).

The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for vitamin C is based on the amount of vitamin C intake necessary to maintain neutrophil vitamin C concentration with minimal urinary excretion of vitamin C and is proposed to provide sufficient antioxidant protection (**Table 2**) (35). The recommended intake for smokers is 35 mg/day higher than for nonsmokers, because smokers are under increased oxidative stress from the toxins in cigarette smoke and generally have lower blood concentrations of vitamin C (36).

Table 2. Recommended Dietary Allowance (RDA) for Vitamin C

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	40 (AI)	40 (AI)
Infants	7-12 months	50 (AI)	50 (AI)
Children	1-3 years	15	15
Children	4-8 years	25	25
Children	9-13 years	45	45
Adolescents	14-18 years	75	65
Adults	19 years and older	90	75
Smokers	19 years and older	125	110
Pregnancy	18 years and younger	-	80
Pregnancy	19 years and older	-	85
Breast-feeding	18 years and younger	-	115
Breast-feeding	19 years and older	-	120

Disease Prevention

The amount of vitamin C required to help prevent chronic disease is higher than the amount required for prevention of scurvy. Information regarding vitamin C and the prevention of chronic disease is based on both observational prospective cohort studies and randomized controlled trials (29, 37). Prospective cohort studies can examine the incidence of a specific disease in relation to vitamin C intake or body status in a cohort of participants who are followed over time. In contrast, trials are intervention studies that can establish a causal relationship between an exposure and an outcome, e.g., by evaluating the effect of vitamin C supplementation on the incidence of chronic disease in participants randomly assigned to receive either vitamin C or placebo for a given length of time.

Cardiovascular disease

Endothelial dysfunction

Endothelial dysfunction is considered to be an early step in the development of atherosclerosis. Alterations in the structure and function of the vascular endothelium that lines the inner surface of all blood vessels are associated with the loss of normal nitric oxide-mediated endothelium-dependent vasodilation. Endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities. The measurement of brachial artery flow-mediated dilation (FMD) is often used as a functional marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (38). A 2014 meta-analysis of 44 randomized controlled trials in subjects with or without chronic diseases summarized the effect of supplemental vitamin C on endothelial function by measuring FMD (19 studies), assessing forearm blood flow (20 studies), or by pulse wave analysis (5 trials) (39). Short-term supplementation with vitamin C was found to reduce endothelial dysfunction in subjects with heart failure, atherosclerosis, or diabetes mellitus, but it had no effect in those with hypertension. Vitamin C also limited endothelial dysfunction that was experimentally induced in healthy volunteers (39). Improved endothelial function was observed with daily vitamin C doses above 500 mg (39).

Hypertension

Hypertension is a major risk factor for cardiovascular disease, including coronary heart disease, stroke, and atrial fibrillation. An analysis that combined data from three, large, independent prospective cohorts, (1) Nurses' Health Study 1 (NHS1; 88,540 women, median age 49 years); (2) Nurses' Health Study 2 (NHS2; 97,315 women, median age 36 years); and (3) Health Professionals Follow-up Study (HPFS; 37,375 men, median age 52 years), found no association between the level of vitamin C intake and risk of developing hypertension (40). On the other hand, when plasma vitamin C concentration was measured, cross-sectional studies have consistently indicated an inverse relationship between plasma vitamin C concentration and blood pressure in both men and women (41-43). A 15-year follow-up of about 2,500 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study found that higher plasma vitamin C and a higher diet quality score were independently associated with a reduced risk of developing hypertension (44). Interestingly, there was no relationship between diet score and risk of hypertension in those with the lowest plasma vitamin C, and plasma vitamin C was positively associated with risk of hypertension in those with low diet scores (44).

A meta-analysis of 29 small randomized controlled trials of short durations (median duration, 8 weeks) in 1,407 participants (10 to 120 subjects per trial; including both normotensive and hypertensive subjects) found that daily supplementation with 60 to 4,000 mg of vitamin C (median dose, 500 mg) reduced systolic blood pressure by 3.84 mm Hg and diastolic blood pressure by 1.48 mm Hg (45). Good quality long-term trials are needed to examine whether the anti-hypertensive effect of vitamin C is sustained over time and eventually results in a reduced risk of cardiovascular events.

It is important for individuals with significantly elevated blood pressure not to rely on vitamin C supplementation alone to reduce their hypertension. They should instead seek or continue treatment with anti-hypertensive medication and make dietary and lifestyle changes in consultation with their health care provider.

Cardiovascular disease risk

Coronary heart disease (CHD) is characterized by the buildup of plaque inside the arteries that supply blood to the heart (atherosclerosis). Over years of buildup and accumulated damage to the coronary arteries, CHD may culminate in a myocardial infarction or heart attack. Many prospective cohort studies have examined the relationship between vitamin C intake from diet and supplements and CHD risk, the results of which have been pooled and analyzed in two separate analyses (46, 47). In 2004, a pooled analysis of nine prospective cohort studies found that supplemental vitamin C intake (≥400 mg/day for a mean of 10 years), but not dietary vitamin C intake, was inversely associated with CHD risk (46). Conversely, a 2008 meta-analysis of 14 cohort studies concluded that dietary, but not supplemental, vitamin C intake was inversely related to CHD risk (47). The most recent large prospective cohort study found an inverse association between dietary vitamin C intake and CHD mortality in Japanese women, but not in men (48). In spite of the variable association depending on source, these analyses indicate an overall inverse association between higher vitamin C intakes and CHD risk.

Limitations inherent to dietary assessment methodology, such as recall bias, measurement error, and residual confounding, may account for some of the inconsistent associations between vitamin C intake and CHD risk. In order to overcome such limitations, some prospective studies measured plasma or serum concentrations of vitamin C as a more reliable index of vitamin C intake and biomarker of body vitamin C status.

The European Investigation into Cancer and Nutrition (EPIC)-Norfolk prospective cohort study investigated the relationship between vitamin C status and incident heart failure in healthy adults (9,187 men and 11,112 women, aged 58.1+/-9.2 years) (49). After a mean follow-up of 12.8 years, plasma vitamin C was inversely associated with incident cases of heart failure. Specifically, plasma vitamin C ranged from approximately 23 to 70 µmol/L in men and 33 to 82 µmol/L in women; across this range, every 20 µmol/L increase in plasma vitamin C was associated with a 9% reduction in risk of heart failure. Although a primary source of dietary vitamin C, consumption of fruit and vegetables — assessed by food frequency questionnaire — was not found to be associated with a lower risk of congestive heart failure (49). This highlights the fact that limitations associated with dietary assessment methods such as food frequency questionnaires may be overcome by using biomarkers of nutrient intake (50, 51).

A 2017 review of eight published randomized controlled trials found inconsistent results from seven trials reporting on the effect of vitamin C supplementation on serum cholesterol and triglycerides, established risk factors for cardiovascular disease (52). Only one large trial in more than 14,000 older men participating in the Physicians' Health Study II (PHS II) reported on cardiovascular outcomes. PHS II found that vitamin C supplementation (500 mg/day) for an average of eight years had no significant effect on major cardiovascular events, total myocardial infarction, or cardiovascular mortality (53). Notably, this study had several limitations (54), including no measurement of vitamin C status and the recruitment of a well-nourished study population.

There is a need for better quality studies to examine the effect of vitamin C on cardiovascular endpoints in participants with elevated risk of cardiovascular disease.

Stroke

A cerebrovascular event, or stroke, can be classified as hemorrhagic or ischemic. Hemorrhagic stroke occurs when a weakened blood vessel ruptures and bleeds into the surrounding brain tissue. Ischemic stroke occurs when an obstruction within a blood vessel blocks blood flow to the brain. Most (~80%) cerebrovascular events in high-income countries are ischemic in nature and associated with atherosclerosis as an underlying condition (55, 56).

With respect to vitamin C and cerebrovascular disease, a prospective cohort study that followed more than 2,000 residents of a rural Japanese community for 20 years found that the risk of stroke in those with the highest serum concentrations of vitamin C was 29% lower than in those with the lowest serum concentrations of vitamin C (57). Similarly, the EPIC-Norfolk study, a 10-year prospective cohort study in 20,649 adults, found that individuals with plasma vitamin C concentrations in the top quartile (25%) had a 42% lower risk of stroke compared to those in the lowest quartile (≥66 µmol/L vs. <41 µmol/L) (58). In both the Japanese (57) and EPIC-Norfolk (58) populations, blood vitamin C concentrations were highly correlated with fruit and vegetable intake. Therefore, as in many studies of vitamin C intake and chronic disease risk, it is difficult to separate the effects of vitamin C from the effects of other components of fruit and vegetables. For example, potassium — found at high levels in bananas, potatoes, and other fruit and vegetables — is known to be important in blood pressure regulation, and elevated blood pressure is a major risk factor for stroke (see the article on Potassium). A 2013 meta-analysis of 17 prospective cohort studies reported a 19% lower risk of stroke with the highest versus lowest dietary vitamin C intakes and a 38% lower risk with the highest versus lowest circulating vitamin C concentrations (59).

A randomized, double-blind, placebo-controlled trial in more than 14,000 older men participating in the Physicians' Health Study II (PHS II) found that vitamin C supplementation (500 mg/day) for an average of eight years had no significant effect on the incidence of or mortality from any type of stroke (53). Other trials also failed to show any evidence of an effect of vitamin C on the risk of stroke. A meta-analysis of 10 trials that examined antioxidant vitamins, of which five included vitamin C, found no association between any antioxidant vitamin (vitamin C, vitamin E, or β-carotene), administered alone or in combination, and risk of stroke (60).

Cancer

Overall, observational prospective cohort studies have reported no or modest inverse associations between vitamin C intake and the risk of developing a given type of cancer (37, 61-63). Additional detail is provided below for those cancer subtypes with substantial scientific information obtained from prospective cohort studies. Randomized, double-blind, placebo-controlled trials that have tested the effect of vitamin C supplementation (alone or in combination with other antioxidant nutrients) on cancer incidence or mortality have shown no effect (64).

Breast cancer

Two large prospective studies found dietary vitamin C intake to be inversely associated with breast cancer incidence in certain subgroups. In the Nurses' Health Study, premenopausal women with a family history of breast cancer who consumed an average of 205 mg/day of vitamin C from food had a 63% lower risk of breast cancer than those who consumed an average of 70 mg/day (65). In the Swedish Mammography Cohort, overweight women who consumed an average of 110 mg/day of vitamin C had a 39% lower risk of breast cancer compared to overweight women who consumed an average of 31 mg/day (66). More recent prospective cohort studies have reported no association between dietary and/or supplemental vitamin C intake and breast cancer (67-69).

Stomach cancer

A number of observational studies have found increased dietary vitamin C intake to be associated with decreased risk of gastric (stomach) cancer, and laboratory experiments indicate that vitamin C inhibits the formation of carcinogenic N-nitroso compounds in the stomach (70-72). A nested case-control study in the EPIC study found a 45% lower risk of gastric cancer incidence in individuals in the highest (≥51 µmol/L) versus lowest (<29 µmol/L) quartile of plasma vitamin C concentration; no association was observed between dietary vitamin C intake and gastric cancer (73).

Infection with the bacteria, *Helicobacter pylori* (*H. pylori*), is known to increase the risk of stomach cancer and is associated with lower vitamin C content of stomach secretions (74, 75). Although two intervention studies failed to show a reduction in stomach cancer incidence with vitamin C supplementation (35), some research suggests that vitamin C supplementation may be a useful addition to standard *H. pylori* eradication therapy in reducing the risk of gastric cancer (76). Because vitamin C can inactivate urease (an enzyme that facilitates *H. pylori* survival and colonization of the gastric mucosa at low pH) *in vitro*, vitamin C may be most effective as a prophylactic agent in those without achlorhydria (77, 78).

Colon cancer

By pooling data from 13 prospective cohort studies comprising 676,141 participants, it was determined that dietary intake of vitamin C was not associated with colon cancer, while total intake of vitamin C (i.e., from food and supplements) was associated with a 19% reduced risk of colon cancer (79). Each of the cohort studies used self-administered food frequency questionnaires at baseline to assess vitamin C intake. Although the analysis adjusted for several lifestyle and known risk factors, the authors noted that other healthy behaviors and/or folate intake may have confounded the association.

Non-Hodgkin lymphoma

A population-based, prospective study, the Iowa Women's Health Study, collected baseline data on diet and supplement use in 35,159 women (aged 55-69 years) and evaluated the risk of developing non-Hodgkin lymphoma (NHL) over 19 years of follow-up (80). Overall, an inverse association between fruit and vegetable intake and risk of NHL was observed. Additionally, dietary, but not supplemental, intake of vitamin C and other antioxidant nutrients (carotenoids, proanthocyanidins, and manganese) was inversely associated with NHL risk. Another large, multi-center, prospective study — the Women's Health Initiative — that followed 154,363 postmenopausal women for 11 years found that dietary and supplemental vitamin C intake at baseline was inversely associated with diffuse B-cell lymphoma, a subtype of NHL (81).

Other site-specific cancer types

The Physicians' Health Study II was a randomized, placebo-controlled trial that examined the effect of vitamin E (400 IU/day), vitamin C (500 mg/day), and a multivitamin supplement on the risk of cancer in 14,641 middle-aged male physicians over 10.3 years (7.6 years of active treatment plus 2.8 years post-treatment follow-up) (82). Supplementation with vitamin C had no effect on the overall risk of cancer or on the risk of prostate, bladder, or pancreatic cancer; there was a marginal reduction in colorectal cancer incidence with vitamin C compared to placebo (82).

Type 2 diabetes mellitus

In the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health study that included 232,007 participants, the use of vitamin C supplements for at least seven times a week was associated with a 9% lower risk of developing type 2 diabetes mellitus compared to non-supplement use (83). In a cohort of 21,831 adults followed for 12 years in the EPIC-Norfolk study, high plasma vitamin C was found to be strongly associated with a reduced risk of diabetes (84). Additionally, several cross-sectional studies reported inverse associations between circulating vitamin C concentrations and markers of insulin resistance or glucose intolerance, such as glycated hemoglobin (HbA1c) concentration (50, 85, 86). Yet, short-term randomized controlled studies have found no effect of vitamin C supplementation on fasting glucose, fasting insulin, and HbA1c concentrations in healthy individuals (87). It is not known whether supplemental vitamin C could improve markers of glycemic control in subjects at risk of diabetes.

Adverse pregnancy outcomes

A 2015 meta-analysis of 29 randomized controlled trials found that administration of vitamin C during pregnancy, alone or in combination with a few other supplements, failed to reduce the risks of stillbirth, perinatal death, intrauterine growth restriction, preterm birth, premature rupture of membranes, and preeclampsia (88). Nonetheless, vitamin C supplementation led to a 36% lower risk of placental abruption and to a significant increase in gestational age at birth (88). Another meta-analysis of 40 randomized controlled trials in 276,820 women found no effect of vitamin C, alone or combined with vitamin E or multivitamins, when supplemented during pregnancy (starting prior to 20 weeks' gestation), on the risks of overall fetal loss, miscarriage, stillbirth, and congenital malformation (89).

Cigarette smoking during pregnancy causes intrauterine growth restriction and preterm birth, among other pregnancy complications (90, 91), and is the primary cause of childhood respiratory illness (92). For some still unclear reasons, smoking has been associated with a lower risk of preeclampsia during pregnancy (93). A secondary analysis of a multicenter, randomized, double-blind, placebo-controlled trial in nearly 10,000 pregnant women found no reduction in the risk of preeclampsia with supplemental vitamin C (1,000 mg/day) and vitamin E (400 IU/day), regardless of women's smoking status during pregnancy. However, antioxidant supplementation resulted in reduced risks of placental abruption and preterm birth in women who smoked during pregnancy but not in non-smokers (94). Another pilot multicenter trial found better lung function during the first week of life and lower risk of wheezing through one year of age in infants whose smoking mothers were randomized to receive vitamin C (500 mg/day) rather than a placebo during pregnancy (95). The Vitamin C to Decrease the Effects of Smoking in Pregnancy on Infant Lung Function [VCSIP] study is an ongoing trial designed to confirm these preliminary observations using more accurate measurements of pulmonary function in a larger sample of women randomized to receive supplemental vitamin C or placebo (96).

Alzheimer's disease

In the US, Alzheimer's disease (AD) is the most common form of dementia, affecting 5.5 million individuals 65 years and over (97). Oxidative stress, neuroinflammation, β-amyloid plaque deposition, Tau protein-forming tangles, and neuronal cell death in the brain of subjects affected by AD have been associated with cognitive decline and memory loss. Lower vitamin C concentrations in the cerebrospinal fluid (CSF) and brain extracellular matrix of a mouse model of AD were found to increase oxidative stress and accelerate amyloid deposition and disease progression (98). In another AD mouse model that was lacking the ability to synthesize vitamin C, supplementation with a high versus low dose of vitamin C reduced amyloid deposition in the cortex and hippocampus and limited blood-brain barrier impairments and mitochondrial dysfunction (99).

The majority of large, population-based studies examining the relationship of vitamin C intake or supplementation with AD incidence have reported null results (100). In contrast, observational studies reported lower plasma vitamin C concentrations in AD patients compared to cognitively healthy subjects (101) and found better cognitive function or lower risk of cognitive impairment with higher plasma vitamin C (100).

Few studies have measured vitamin C concentration in the CSF, which more closely reflects the vitamin C status of the brain. Vitamin C is concentrated in the brain through a combination of active transport into brain tissue and retention via the blood-brain barrier (100). Although CSF vitamin C is maintained at concentrations several-fold higher than plasma vitamin C, the precise function of vitamin C in cognitive function and AD etiology is not yet fully understood (102). In a small, longitudinal biomarker study in 32 individuals with probable AD, a higher CSF-to-plasma vitamin C ratio at baseline was associated with a slower rate of cognitive decline at one year of follow-up (103). Impaired blood-brain barrier integrity may affect the brain's ability to retain vitamin C and thus to maintain a high CSF-to-plasma vitamin C ratio. The significance of the CSF-to-plasma vitamin C ratio in AD progression requires further study.

The effect of vitamin C supplementation, in combination with other antioxidants, on CSF biomarkers and cognitive function has been examined in only a few trials involving AD patients. In a small (n=23), open-label trial, combined supplementation with vitamin C (1,000 mg/day) and vitamin E (400 IU/day) to AD patients taking a cholinesterase inhibitor significantly increased antioxidant levels and decreased lipoprotein oxidation in CSF after one year, but had no effect on the clinical course of AD compared to controls (104). A similar finding was obtained in a double-blind, randomized controlled trial in which combined supplementation with vitamin C (500 mg/day), vitamin E (800 IU/day), and α-lipoic acid (900 mg/day) for 16 weeks reduced lipoprotein oxidation in CSF but elicited no clinical benefit in individuals with mild-to-moderate AD (n=78) (105). In this latter trial, a greater decline in the Mini Mental State Examination (MMSE) score was observed in the supplemented group, however, the significance of this observation remains unclear. A third placebo-controlled trial in mildly cognitively impaired older adults (ages, 60-75 years) found that one-year supplementation with vitamin C (400 mg/day) and vitamin E (300 mg/day) improved antioxidant blood capacity but had no effect on MMSE scores (106).

At this time, avoidance of vitamin C deficiency or insufficiency, rather than supplementation in replete individuals, seems prudent for the promotion of healthy brain aging (101).

Cataracts

The lens of the eye focuses light, producing a clear, sharp image on the retina, a layer of tissue on the inside back wall of the eyeball. Age-related changes to the lens (thickening, loss of flexibility) and oxidative damage contribute to the formation of cataract, i.e., cloudiness or opacity in the lens that interferes with the clear focusing of images on the retina.

In humans, vitamin C concentration is about 15 to 20 times higher in the aqueous humor — fluid that fills the anterior and posterior chambers of the eye — than in plasma, suggesting that the vitamin may be playing an important role in the eye (107). Decreased vitamin C concentrations in the lens of the eye have been associated with increased severity of cataracts (108). A meta-analysis of observational studies found that a reduced risk of age-related cataract with higher dietary vitamin C intakes in case-control studies and with higher circulating vitamin C concentrations in cross-sectional studies. However, no such associations were found in pooled analyses of prospective cohort studies (109). In fact, two prospective cohort studies in Swedish men (110) and women (111) reported that high-dose single nutrient supplements of vitamin C were associated with an increased risk of cataract, especially in those on corticosteroid therapy.

A 2012 review of nine randomized controlled trials found no substantial effect of β-carotene, vitamin C, and vitamin E, administered individually or in combination over 2.1 to 12 years, on the risk of cataracts or cataract surgery (112). Although trials do not currently support the use of high-dose supplementation with vitamin C in cataract prevention, there is a consistent inverse association observed between high daily intake of fruit and/or vegetables (>5 servings/day) and risk of cataract (113).

Gout

Gout, a condition that afflicts more than 4% of US adults (114), is characterized by abnormally high blood concentrations of uric acid (urate) (115). Urate crystals may form in joints, resulting in inflammation and pain, as well as in the kidneys and urinary tract, resulting in kidney stones. The tendency to exhibit elevated blood uric acid concentrations and develop gout is often inherited; however, dietary and lifestyle modification may be helpful in both the prevention and treatment of gout (116). In an observational study that included 1,387 men, higher intakes of vitamin C were associated with lower serum concentrations of uric acid (117). In a cross-sectional study conducted in 4,576 African Americans, the odds of having hyperuricemia was associated with dietary intakes high in fructose, low in vitamin C, or with high fructose-to-vitamin C ratios (118). A prospective study that followed a cohort of 46,994 men for 20 years found that total daily vitamin C intake was inversely associated with incidence of gout, with higher intakes being associated with greater risk reductions (119). The results of this study also indicated that supplemental vitamin C may be helpful in the prevention of gout (119).

A 2011 meta-analysis of 13 randomized controlled trials in healthy individuals with elevated serum uric acid revealed that vitamin C supplementation (a median dose of 500 mg/day for a median duration of 30 days) modestly reduced serum uric acid concentrations by 0.35 mg/dL compared to placebo (120). Such a reduction falls within the range of assay variability and is unlikely to be clinically significant (121). An eight-week, open-label, controlled trial randomized 40 subjects with gout to receive either allopurinol (standard-of-care), vitamin C, or both treatments (122). The effect of vitamin C, alone or with allopurinol, decreasing serum uric acid was modest and much less than that of allopurinol alone. The trial did not examine the effect of vitamin C on other outcomes associated with gout (122).

Although observational studies suggested that supplemental vitamin C may be helpful to prevent incident and recurrent gout, this has not been demonstrated by intervention studies undertaken thus far. In addition, there is currently little evidence to support a role for vitamin C in the management of patients with gout (123).

Mortality

Two large prospective cohort studies assessed the relationship between dietary and supplemental vitamin C intakes and mortality. In the Vitamins and Lifestyle Study, 77,719 men and women (ages 50-76 years) were questioned at baseline on their use of dietary supplements during the previous 10 years (124). After five years of follow-up, vitamin C supplement use was associated with a small decreased risk of total mortality, although no association was found with cardiovascular disease- or cancer-specific mortality. In the second prospective cohort study, the Diet, Cancer and Health Study, 55,543 Danish adults (ages 50-64 years) were questioned at baseline about their lifestyle, diet, and supplement use during the previous 12 months (125). No association between dietary or supplemental intake of vitamin C and mortality was found after approximately 14 years of follow-up. In contrast, a 2014 meta-analysis of 10 prospective cohort studies in 17,696 women with breast cancer found a lower risk of total and breast cancer-specific mortality with higher supplemental and dietary vitamin C intakes (126). A 2012 meta-analysis of 29 trials found no effect of oral vitamin C, given alone or in combination with other antioxidants, on all-cause mortality (127).

In parallel to these dietary assessment studies, a strong inverse association between plasma vitamin C and mortality from all-causes, cardiovascular disease, and ischemic heart disease (and cancer in men only) was observed in the EPIC-Norfolk multicenter, prospective cohort study (128). After approximately four years of follow-up in 19,496 men and women (ages 45-79 years), a dose-response relationship was observed such that each 20 µmol/L increase in plasma vitamin C was associated with an estimated 20% risk reduction in all-cause mortality. Similarly, higher serum vitamin C concentrations were associated with decreased risks of cancer-specific and all-cause mortality in 16,008 adults from the US National Health and Nutrition Examination Survey (NHANES) III (1994-1998) (129).

Disease Treatment

Cardiovascular disease

Complications of cardiac procedures and surgeries

Periprocedural myocardial injury: Coronary angioplasty (also called percutaneous transluminal coronary angioplasty) is a nonsurgical procedure for treating obstructive coronary heart disease (CHD), including unstable angina pectoris, acute myocardial infarction, and multivessel CHD. Angioplasty involves temporarily inserting and inflating a tiny balloon into the clogged artery to help restore the blood flow to the heart. Periprocedural myocardial injury that occurs in up to one-third of patients undergoing otherwise uncomplicated angioplasty increases the risk of morbidity and mortality at follow-up.

One randomized, placebo-controlled trial has examined the effect of intravenous vitamin C administered to patients with stable angina undergoing elective coronary angioplasty (130). Administration of a 1-gram (g) vitamin C infusion one hour prior to the angioplasty reduced the concentrations of oxidative stress markers and improved microcirculatory perfusion compared to placebo (130). Another trial randomized 532 patients to receive a 3-g vitamin C infusion or a placebo (saline solution) within six hours prior to coronary angioplasty (131). Vitamin C treatment substantially reduced the incidence of periprocedural myocardial injury, as assessed by a reduction in the concentrations of two markers of myocardial injury, namely creatine kinase and troponin-I (131). A recent randomized controlled trial assessed the effect of vitamin C and vitamin E administration on reperfusion damage in patients who experienced acute myocardial infarction and underwent coronary angioplasty (see below) (132).

Myocardial reperfusion injury: Reperfusion injury refers to tissue damage occurring at the time of blood flow restoration (reperfusion) following transient ischemia. The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction or with aortic clamping during coronary artery bypass graft (CABG) surgery. Increased generation of reactive oxygen species (ROS) when the heart muscle's oxygen supply is restored might be an important contributor to myocardial damage occurring at reperfusion (133). Myocardial reperfusion injury leads to complications, such as reperfusion arrhythmias (see Atrial fibrillation) and myocardial stunning.

Vitamin C is depleted during and following cardiac surgery (134) and this might be due to the direct quenching of ROS, the regeneration of other antioxidants, and/or a massive synthesis of catecholamines (dopamine, epinephrine, norepinephrine) (135). Two randomized controlled trials conducted in the 1990s reported a reduction in reperfusion-induced oxidative stress and myocardial injury with intravenous (136) or oral (137) vitamin C administration prior to CABG surgery (reviewed in 135). A more recent randomized, double-blind, placebo-controlled trial has been designed to examine the effect of vitamin C and vitamin E administration on ischemia-reperfusion damage in 99 patients with acute myocardial infarction undergoing coronary angioplasty (132). Vitamin C infusion (sodium ascorbate: 3.20 mmol/min for 1 hour then 0.96 mmol/min for 2 hours) prior to reperfusion followed by oral supplementation with vitamin C (1 g/day) and vitamin E (400 IU/day) for 84 days effectively prevented a reduction in antioxidant capacity at reperfusion and for the next six to eight hours. The protocol also limited microvascular dysfunction (i.e., improved microcirculatory perfusion) and improved left ventricular ejection fraction at discharge (on day 84) (138, 139). However, no difference in the infarct size between antioxidant vitamin treatment and placebo was seen (138).

Atrial fibrillation: Atrial fibrillation is the most common type of cardiac arrhythmia. It is also a common post-cardiac surgery complication, leading to an increased risk of cardiovascular morbidity (e.g., heart failure, stroke) and mortality. Three meta-analyses of prospective cohort studies and randomized controlled trials have reported an overall reduction in the risk of post-operative atrial fibrillation following administration of primarily oral vitamin C (140-142). In most trials, participants received 2 g of vitamin C prior to undergoing CABG or valve replacement surgery and 1 to 2 g/day for five days post-surgery. Although only a minority of trials delivered vitamin C intravenously, this administration route appeared to be more effective at reducing the risk of atrial fibrillation — presumably due to higher plasma concentrations achieved (140). Of note, a subgroup analysis in one of the meta-analyses showed a reduction of post-operative atrial fibrillation with vitamin C in non US-based trials (10 trials) but no effect of vitamin C in US-based trials (5 trials) (140).

Cerebral ischemia-reperfusion injury

A small randomized controlled trial performed in 60 ischemic stroke patients showed that intravenous vitamin C administration (500 mg/day for 10 days, initiated day 1 post-stroke) had no effect on serum markers of oxidative stress or neurological outcomes compared to placebo (143).

Vascular complications of diabetes mellitus

Cardiovascular disease (CVD) is the leading cause of death in individuals with diabetes mellitus. The role of increased oxidative stress in the occurrence of vascular complications in subjects with diabetes has led to hypothesis that higher intakes of antioxidant nutrients could help lower the risk of CVD in diabetic subjects (144). A 2018 meta-analysis of randomized controlled trials investigating the effect of antioxidant vitamin supplementation in patients with type 2 diabetes found that most improvement in markers of oxidative stress and blood glucose control could be attributed to vitamin E (145). Another meta-analysis of trials found no effect of vitamins E and C, alone or in combination, on measures of β-cell function and insulin resistance (146). Yet, most studies were small and of short duration and thus did not assess the consequence of long-term use of antioxidant vitamins on the risk of vascular complications in diabetic patients. One 12-month randomized placebo-controlled trial in 456 participants with type 2 diabetes treated with metformin examined the effect of vitamin C (500 mg/day) or acetylsalicylic acid (aspirin; 100 mg/day) on risk factors for diabetes-related complications such as CVD (147). Both vitamin C and aspirin reduced fasting blood glucose and HbA1c concentrations and improved blood lipid profile in metformin-treated patients. Compared to placebo, both treatments were found to be more likely to limit risk factors contributing to diabetes-related complications, as well as to lower the risk of future cardiovascular events over a 10-year period (estimated using the Framingham risk score) (147).

Of note, it is possible that genetic differences among diabetic patients influence the effect of vitamin C supplementation on cardiovascular risk. In particular, a specific allele of the haptoglobin gene (Hp), namely Hp2, appears to be associated with an increased risk of diabetic vascular complications. Carriers of two copies of the Hp2 allele (Hp2-2) express a Hp protein that has a lower capacity to bind and remove pro-oxidant, free hemoglobin (Hb) from plasma, compared to Hp proteins coded by the Hp1-1 and Hp1-2 genotypes. When the results of the Women's Antioxidant Vitamin Estrogen (WAVE) trial were reanalyzed based on Hp genotype, antioxidant therapy (1,000 mg/day of vitamin C + 800 IU/day of vitamin E) was associated with improvement of coronary atherosclerosis in diabetic women with Hp1-1 genotype but worsening of coronary atherosclerosis in those carrying the Hp2-2 genotype (148). Results from another study by the same investigators suggested that vitamin C could not prevent the oxidation of high-density lipoprotein (HDL)-cholesterol by glycated Hb-Hp2-2 complexes *in vitro* nor restore impaired HDL function in diabetic mice carrying the Hp2-2 genotype (149).

Sepsis

Sepsis and septic shock — defined as persistent sepsis-induced low blood pressure — are associated with elevated mortality rates in critically ill patients (150, 151). Because systemic inflammatory responses involve excessive oxidative stress, it has been suggested that providing antioxidant nutrients like vitamin C may improve the outcome of critically ill patients in intensive care units. In addition, hypovitaminosis C is common in critically ill patients, especially in those with septic shock, and persists despite enteral/parenteral nutritional therapy providing recommended amounts of vitamin C (152). Vitamin C requirements are likely to be increased in this population due to the hypermetabolic response driven by the systemic inflammatory reaction (152, 153). Intravenous administration of 50 mg or 200 mg of vitamin C per kg per day for 96 hours to patients with sepsis admitted in intensive care unit was found to correct vitamin C deficiency. Vitamin C also prevented the rise of Sequential Organ Failure Assessment (SOFA) and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores — used to assess severity of illness and risk of mortality — observed in placebo-treated patients (154). Vitamin C infusion also lowered the concentration of markers of inflammation and endothelial injury in patients compared to placebo (154). In another randomized, double-blind, controlled trial in 28 critically ill patients with septic shock, infusion of 25 mg of vitamin C per kg every six hours for 72 hours significantly limited the requirement to vasopressor norepinephrine — decreasing both the dose and duration of treatment — and dramatically improved the 28-day survival rate (155). Similar results have been reported in septic patients given intravenous vitamin C (1.5 g/6 h), hydrocortisone (50 mg/6 h), and thiamin (200 mg/12 h) until hospital discharge. Compared to standard-of-care, this intervention cocktail more than halved the mean duration of vasopressor use (18.3 h versus 54.9 h) and reduced the odds of mortality by nearly 90% (156). Although intravenous vitamin C administration appears to be safe and well tolerated, there is a non-negligible risk of oxalate nephropathy (a rare cause of kidney failure) in these critically ill patients (157).

See also the section on Sepsis in the Symposium on Vitamin C — Part of the LPI's 9th International Conference on Diet and Optimum Health.

Cancer

Route of administration

Studies in the 1970s and 1980s conducted by Linus Pauling, Ewan Cameron, and colleagues suggested that large doses of vitamin C (10 g/day infused intravenously for 10 days followed by at least 10 g/day orally indefinitely) were helpful in increasing the survival time and improving the quality of life of terminal cancer patients (158). Controversy surrounding the efficacy of least 10 g/day orally indefinitely) were helpful in increasing the survival time and improving the quality of life of terminal cancer patients (158). Controversy surrounding the efficacy of vitamin C in cancer treatment ensued, leading to the recognition that the route of vitamin C administration is critical (22, 159). Compared to orally administered vitamin C, intravenous vitamin C can result in 30 to 70-fold higher plasma vitamin C concentrations (25). Higher plasma concentrations achieved via intravenous vitamin C administration are comparable to those that are toxic to cancer cells in culture. The anticancer mechanism of intravenous vitamin C action is under investigation. It may involve the production of high levels of hydrogen peroxide, selectively toxic to cancer cells (22, 160-162), or the deactivation of hypoxia inducible factor, a prosurvival transcription factor that protects cancer cells from various forms of stress (159, 163, 164). Vitamin C likely also plays a role in the maintenance of genome integrity and in the protection against cellular transformation through regulating DNA and histone demethylating enzymes (see Function) (165).

Safety

Current evidence from controlled clinical trials indicates that intravenous vitamin C is generally safe and well tolerated in cancer patients. Of note, because intravenous administration of 80 g of vitamin C precipitated hemolytic anemia in two subjects with glucose-6-phosphate dehydrogenase deficiency, patients due to receive high-dose vitamin C infusion are systematically screened for this genetic disorder (166). Four phase I clinical trials in patients with advanced cancer found that intravenous administration of vitamin C at doses up to 1.5 g/kg of body weight (equivalent to about 100 g/day for an average weight [70 kg] person) and 70 to 80 g/m^2 was well tolerated and safe in pre-screened patients (167-170). A few observational studies in cancer patients undergoing chemotherapy and/or radiotherapy reported that complementary intravenous vitamin C treatment was associated with a reduction in treatment-associated side effects and an improved quality of life (171). A phase I study in nine patients with metastatic pancreatic cancer showed that millimolar concentrations of plasma vitamin C could be reached safely when administered in conjunction with the cancer chemotherapy drugs, gemcitabine and erlotinib (168).

Sensitivity to vitamin C

Retrospective *in vitro* colony formation assays revealed that patient leukemic cells displayed variable sensitivity to vitamin C treatment: leukemic cells from seven out of the nine patients who experienced a significant clinical benefit were sensitive to vitamin C *in vitro* (i.e., "responders"); the leukemic cells from the remaining six patients were not sensitive to vitamin C (i.e., "non-responders"). Thus, *in vitro* vitamin C sensitivity assays may provide predictive value for the clinical response to intravenous vitamin C treatment. The mechanisms underlying differential sensitivity to vitamin C are under investigation. *In vitro* experiments performed using 11 different cancer cell lines demonstrated that sensitivity to vitamin C correlated with the expression of catalase, an enzyme involved in the decomposition of hydrogen peroxide (172). Approximately one-half of the cell lines tested were resistant to vitamin C cytotoxicity, a response associated with high levels of catalase activity.

Sensitivity to vitamin C may also be determined by the expression of sodium-dependent vitamin C transporter-2 (SVCT-2), which transports vitamin C into cells (173). Higher SVCT-2 levels were associated with enhanced sensitivity to vitamin C in nine different breast cancer cell lines. Moreover, SVCT-2 was significantly expressed in 20 breast cancer tissue samples, but weakly expressed in normal tissues. Finally, mutations in genes coding for vitamin C-dependent TET demethylases, mutations that are common in cancer cells, may also contribute to resistance to vitamin C treatment (165).

Efficacy

Current evidence of the efficacy of intravenous vitamin C in cancer patients is limited to observational studies, uncontrolled interventions, and case reports (174, 175). There is a need for larger, longer-duration phase II clinical trials that test the efficacy of intravenous vitamin C in disease progression and overall survival (176).

See also the section on Cancer in the Symposium on Vitamin C — Part of the LPI's 9th International Conference on Diet and Optimum Health.

Common cold

The work of Linus Pauling stimulated public interest in the use of doses greater than 1 g/day of vitamin C to prevent the common cold (177). In the past 40 years, numerous placebo-controlled trials have examined the effect of vitamin C supplementation on the prevention and treatment of colds. A 2013 meta-analysis of 53 placebo-controlled trials evaluated the effect of vitamin C supplementation on the incidence, duration, or severity of the common cold when taken as a continuous daily supplement (43 trials) or as therapy upon onset of cold symptoms (10 trials) (178). Regarding the incidence of colds, a difference was observed between two groups of participants. Regular supplementation with vitamin C (0.25 to 2 g/day) did not reduce the incidence of colds in the general population (23 trials); however, in participants undergoing heavy physical stress (e.g., marathon runners, skiers, or soldiers in subarctic conditions), vitamin C supplementation halved the incidence of colds (5 trials). A benefit of regular vitamin C supplementation was also seen in the duration of colds, with a greater benefit in children than in adults: The pooled effect of vitamin C supplementation was a 14% reduction in cold duration in children and an 8% reduction in adults. Finally, no significant effect of vitamin C supplementation (1-8 g/day) was observed in therapeutic trials in which vitamin C was administered after cold symptoms occurred.

In addition, a 2013 systematic review by the same investigators identified only two small randomized, double-blind, placebo-controlled trials that examined the effect of vitamin C on the incidence of respiratory infection-induced asthma (179). One trial found that vitamin C supplementation (1 g/day) for 14 weeks reduced the risk of asthma attacks precipitated by respiratory infection. The other trial randomized subjects diagnosed with infection-related asthma to receive 5 g/day of vitamin C or a placebo for one week; a lower proportion of participants was found to present with bronchial hypersensitivity to histamine — which characterizes chronic asthma — in the vitamin C group compared to the control group (reviewed in 179). These observations need to be confirmed in larger, well-designed trials.

Asthma

A 2013 systematic review identified 11 randomized controlled studies that evaluated the effect of vitamin C on asthma (eight trials) or exercise-induced bronchoconstriction (three trials) (180). Exercise-induced bronchoconstriction is a transient narrowing of the airways that occurs after exercise and is indicated by a ≥10% decline in Forced Expiratory Volume in 1 second (FEV_1). In the three trials that included a total of 40 participants with exercise-induced bronchoconstriction, vitamin C administration before exercise (a 0.5-g dose on two subsequent days in one trial, a single dose of 2 g in the second trial, and 1.5 g daily for two weeks in the third trial) significantly reduced the exercise-induced decline in FEV_1. Among the five out of eight trials in asthmatic subjects that reported on FEV_1 outcomes, none found a difference between vitamin C supplementation and placebo (180).

Lead toxicity

Although the use of lead paint and leaded gasoline has been discontinued in the US, lead toxicity continues to be a significant health problem, especially in children living in urban areas. Abnormal growth and development have been observed in infants of women exposed to lead during pregnancy, while children who are chronically exposed to lead are more likely to develop learning disabilities, behavioral problems, and to have a low IQ. In adults, lead toxicity may result in kidney damage, high blood pressure, and anemia.

Several cross-sectional studies have reported an inverse association between vitamin C status and blood lead concentration. For instance, in a study of 747 older men, blood lead concentration was significantly higher in those who reported total dietary vitamin C intakes averaging less than 109 mg/day compared to those with higher vitamin C intakes (181). A much larger study of 19,578 people, including 4,214 children from 6 to 16 years of age, found higher serum vitamin C concentrations to be associated with significantly lower blood lead concentrations (182). A US national survey of more than 10,000 adults found that blood lead concentrations were inversely related to serum vitamin C concentrations (183).

Cigarette smoking or second-hand exposure to cigarette smoke contributes to increased blood lead concentration and a state of chronic low-level lead exposure. An intervention trial in 75 adult male smokers found that supplementation with 1,000 mg/day of vitamin C resulted in significantly lower blood lead concentration over a four-week treatment period compared to placebo (184). A lower dose of 200 mg/day did not significantly affect blood lead concentration, although serum vitamin C concentrations were not different from those in the group who took 1,000 mg/day.

The mechanism(s) by which vitamin C reduces blood lead concentration is not known, yet it has been proposed that vitamin C could inhibit intestinal absorption (184) or enhance urinary excretion of lead (185).

Sources

Unlike plants and most animals, humans have lost the ability to synthesize vitamin C endogenously and therefore have an essential dietary requirement for this vitamin (see The Recommended Dietary Allowance). Results from 7,277 participants in the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 indicated that an estimated 7.1% of individuals ages ≥6 years were deficient in vitamin C — based on serum vitamin C concentrations <11.4 µmol/L (36). The national study identified smokers and those of lower socioeconomic status to both be at higher risk for vitamin C deficiency (36).

Food sources

As shown in **Table 3**, different fruit and vegetables vary in their vitamin C content, but five servings (2½ cup-equivalents) of a variety of fruit and vegetables should average out to about 150 to 200 mg of vitamin C, especially if vitamin C-rich fruits are consumed. If you wish to check foods for their vitamin C content, search USDA's FoodData Central.

Table 3. Some Food Sources of Vitamin C

Food	Serving	Vitamin C (mg)
Kiwifruit, Zespri SunGold	1 fruit (81 g)	131
Grapefruit juice, pink, raw	¾ cup (6 ounces)	94
Orange juice, raw	¾ cup (6 ounces)	93
Strawberries	1 cup, whole	85
Grapefruit juice, white, raw	¾ cup (6 ounces)	70
Kiwifruit	1 fruit (74 g)	69
Orange	1 medium	65
Sweet red pepper, raw	½ cup, chopped	59
Broccoli, cooked	½ cup	51
Grapefruit, raw	½ medium	44
Brussel sprouts, cooked	½ cup	37
Potato, white, flesh and skin	1 medium, baked	22
Tomato, red, ripe, raw	1 medium	17
Banana, raw	1 medium	10
Apple, raw	1 medium	8
Spinach, raw	1 cup	8

Supplements

Vitamin C (L-ascorbic acid) is available in many forms, but there is little scientific evidence that any one form is better absorbed or more effective than another. Most experimental and clinical research uses ascorbic acid or its sodium salt, called sodium ascorbate. Natural and synthetic L-ascorbic acid are chemically identical and there are no known differences regarding biological activities or bioavailability (186).

Mineral ascorbates

Mineral salts of vitamin C are considered less acidic than vitamin C and therefore are considered "buffered." Some people find them less irritating to the gastrointestinal tract than ascorbic acid. Sodium ascorbate and calcium ascorbate are the most common forms, although a number of other mineral ascorbates are available. Sodium ascorbate provides 111 mg of sodium (889 mg of ascorbic acid) per 1,000 mg of sodium ascorbate, and calcium ascorbate generally provides 90 to 110 mg of calcium (890-910 mg of ascorbic acid) per 1,000 mg of calcium ascorbate.

Vitamin C with flavonoids

Flavonoids are a class of water-soluble plant pigments that are often found in vitamin C-rich fruit and vegetables, especially citrus fruit and berries (see the article on Flavonoids). There is little evidence that the flavonoids in most commercial preparations increase the bioavailability or efficacy of vitamin C (187). Some, yet not all, studies in animal models such as vitamin C-deficient guinea pigs or genetically scorbutic rats found an increased uptake of vitamin C in peripheral circulation and specific organs in the presence of flavonoids. However, studies conducted in humans found no differences in bioavailability of vitamin C from flavonoid-rich whole fruit or fruit juice and synthetic vitamin C (reviewed in 186).

Vitamin C and metabolites

One supplement, Ester-C®, contains mainly calcium ascorbate and includes small amounts of the vitamin C metabolites, dehydroascorbic acid (oxidized ascorbic acid), calcium threonate, and trace amounts of xylonate and lyxonate. Although these metabolites are purported to increase the bioavailability of vitamin C, the only published study in humans addressing this issue found no difference between Ester-C® and commercially available vitamin C tablets with respect to the absorption and urinary excretion of vitamin C (187). Ester-C® should not be confused with ascorbyl palmitate, which is also marketed as "vitamin C ester" (see below).

Ascorbyl palmitate

Ascorbyl palmitate is a vitamin C ester (i.e., ascorbic acid linked to a fatty acid). In this case, vitamin C is esterified to the saturated fatty acid, palmitic acid, resulting in a fat-soluble form of vitamin C. Ascorbyl palmitate has been added to a number of skin creams due to interest in its antioxidant properties, as well as its importance in collagen synthesis (see the separate article, Vitamin C and Skin Health) (188). Although ascorbyl palmitate is also available as an oral supplement, most of it is likely hydrolyzed to ascorbic acid and palmitic acid in the digestive tract before it is absorbed (189). Ascorbyl palmitate is marketed as "vitamin C ester," which should not be confused with Ester-C® (see above).

Other formulations of vitamin C

One small placebo-controlled, cross-over trial in 11 men showed that the oral administration of 4 g of vitamin C resulted in a greater vitamin C concentration in plasma over a four-hour period when vitamin C was encapsulated in liposomes compared to unencapsulated vitamin C (190). Although liposomal encapsulation could increase vitamin C bioavailability, plasma vitamin C concentrations were much lower than those achieved with intravenous vitamin C administration (190).

For a more detailed review of scientific research on the bioavailability of different forms of vitamin C, see The Bioavailability of Different Forms of Vitamin C.

Safety

Toxicity

A number of possible adverse health effects of very large doses of vitamin C have been identified, mainly based on *in vitro* experiments or isolated case reports, and include genetic mutations, birth defects, cancer, atherosclerosis, kidney stones, "rebound scurvy," increased oxidative stress, excess iron absorption, vitamin B_{12} deficiency, and erosion of dental enamel. However, none of these alleged adverse health effects have been confirmed in subsequent studies, and there is no reliable scientific evidence that doses of vitamin C up to 10 g/day in adults are toxic or detrimental to health. The concern of kidney stone formation with vitamin C supplementation is discussed below.

With the latest RDA published in 2000, a tolerable upper intake level (UL) for vitamin C was set for the first time (**Table 4**). A UL of 2 g (2,000 mg) daily was recommended in order to prevent generally healthy adults from experiencing diarrhea and gastrointestinal disturbances (35). Such symptoms are not generally serious, especially if they resolve with temporary discontinuation of vitamin C supplementation.

Table 4. Tolerable Upper Intake Level (UL) for Vitamin C

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	400
Children 4-8 years	650
Children 9-13 years	1,200
Adolescents 14-18 years	1,800
Adults 19 years and older	2,000
*Source of intake should be from foods or formula only.	

Kidney stones

Because oxalate is a metabolite of vitamin C, there is some concern that high vitamin C intake could increase the risk of calcium oxalate kidney stones. Some (24, 191, 192), but not all (193-195), studies have reported that supplemental vitamin C increases urinary oxalate concentrations. Whether any increase in oxalate levels would translate to an elevation in risk for kidney stones has been examined in several epidemiological studies. Two large prospective cohort studies, one following 45,251 men for six years and the other following 85,557 women for 14 years, reported that consumption of ≥1,500 mg of vitamin C daily did not increase the risk of kidney stone formation compared to those consuming <250 mg daily (196, 197). On the other hand, two other large prospective studies reported that a high intake of vitamin C was associated with an increased risk of kidney stone formation in men (198, 199). Specifically, the Health Professionals Follow-Up Study collected data on dietary and supplemental vitamin C intake every four years in 45,619 male health professionals (ages 40-75 years) (198). After 14 years of follow-up, it was found that men who consumed ≥1,000 mg/day of vitamin C had a 41% higher risk of kidney stones compared to men consuming <90 mg of vitamin C daily. In the Cohort of Swedish Men study, self-reported use of single-nutrient vitamin C supplements (taken seven or more times per week) at baseline was associated with a two-fold higher risk of incident kidney stones among 48,840 men (ages 45-79 years) followed for 11 years (199). Despite conflicting results, it may be prudent for individuals predisposed to oxalate kidney stone formation to avoid high-dose vitamin C supplementation.

Drug interactions

Overall, evidence suggesting specific drugs can lower blood vitamin C concentrations in humans is limited. Dihydropyridine calcium channel blockers (e.g., nicardipine, nifedipine) can inhibit vitamin C uptake by intestinal cells *in vitro*. However, a reduction in blood vitamin C concentrations with these drugs has not been reported in humans (200). Aspirin can impair vitamin C status if taken frequently (201).

Conversely, there are case reports suggesting that supplemental vitamin C may lower blood concentrations of some medications, such as fluphenazine (the antipsychotic drug, Prolixin) and indinavir (the antiretroviral drug, Crixivan) (200). There is some evidence, though controversial, that vitamin C interacts with anticoagulant medications like warfarin (Coumadin). Large doses of vitamin C may block the action of warfarin and thus lower its effectiveness. Individuals on anticoagulants should limit their vitamin C intake to <1 g/day and have their prothrombin time monitored by the clinician following their anticoagulant therapy (200). In addition, vitamin C may bind aluminum in the gut and increase the absorption of aluminum-containing compounds (e.g., aluminum-containing antacids, aluminum-containing phosphate binders). People with impaired kidney function may be at risk for aluminum toxicity when supplemental vitamin C is taken at the same time as these compounds (200, 201). Finally, supplemental vitamin C may increase blood estrogen concentrations in women using oral contraceptives or hormone replacement therapy (200).

The potential effect of antioxidants during chemotherapy is not well understood, yet only likely to be an issue if a specific chemotherapeutic agent acts through an oxidative mechanism, which is uncommon (171). It is not clear whether vitamin C given parenterally could diminish or increase the efficacy of chemotherapy drugs — in particular, akylating agents (e.g., cyclophosphamide, busulfan), antitumor antibiotics (e.g., doxorubicin, bleomycin), and arsenic trioxide. Patients are advised to discuss with their oncologist before using vitamin C supplements (200, 201).

Because high doses of vitamin C have also been found to interfere with the interpretation of certain laboratory tests (e.g., serum bilirubin, serum creatinine, and the stool guaiac assay for occult blood), it is important to inform one's health care provider of any recent supplement use.

Antioxidant supplements and HMG-CoA reductase inhibitors (statins)

A three-year randomized controlled trial in 160 patients with documented coronary heart disease and low blood HDL concentrations found that a combination of simvastatin (Zocor) and niacin increased HDL concentration, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, such as myocardial infarction and stroke (202). Surprisingly, when an antioxidant combination (1,000 mg vitamin C, 800 IU vitamin E, 100 μg selenium, and 25 mg β-carotene daily) was taken with the simvastatin-niacin combination, the protective effects were diminished. Since the antioxidants were taken together in this trial, the individual contribution of vitamin C cannot be determined. In contrast, a much larger trial in more than 20,000 men and women with coronary heart disease or diabetes mellitus found that simvastatin and an antioxidant combination (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) did not diminish the cardioprotective effects of simvastatin therapy over a five-year period (203). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplements and cholesterol-lowering drugs, such as HMG-CoA reductase inhibitors (statins).

Does vitamin C promote oxidative damage under physiological conditions?

Vitamin C is known to function as a highly effective antioxidant in living organisms. However, in test tube experiments, vitamin C can interact with some free metal ions and lead to the generation of potentially damaging free radicals. Although free metal ions are not generally found under physiological conditions, the idea that high doses of vitamin C might be able to promote oxidative damage *in vivo* has received a great deal of attention. Widespread publicity has been given to a few studies suggesting a pro-oxidant effect of vitamin C (204, 205), but these studies turned out to be either flawed or of no physiological relevance. A comprehensive review of the literature found no credible scientific evidence that supplemental vitamin C promotes oxidative damage under physiological conditions or in humans (206).

Linus Pauling Institute Recommendation

Combined evidence from metabolic, pharmacokinetic, and observational studies, and from randomized controlled trials supports consuming sufficient vitamin C to achieve plasma concentrations of at least 60 µmol/L. While most generally healthy young adults can achieve these plasma concentrations with daily vitamin C intake of at least 200 mg/day, some individuals may have a lower vitamin C absorptive capacity than what is currently documented. Thus, the Linus Pauling Institute recommends a vitamin C intake of 400 mg daily for adults to ensure replete tissue concentrations (29) — an amount substantially higher than the RDA yet with minimal risk of side effects.

This recommendation can be met through food if the diet includes at least several servings of vitamin C-rich fruit and vegetables (e.g., citrus fruit, kiwifruit, peppers; see Food sources) as part of the daily recommended fruit and vegetable intake (see article on Fruit and Vegetables). Most multivitamin supplements provide at least 60 mg of vitamin C.

Older adults (>50 years)

Whether older adults have higher requirements for vitamin C is not yet known with certainty, yet some older populations have been found to have vitamin C intakes considerably below the RDA of 75 and 90 mg/day for women and men, respectively (207). A vitamin C intake of at least 400 mg daily may be particularly important for older adults who are at higher risk for age-related chronic diseases. Pharmacokinetic studies in older adults have not yet been conducted, but there is some evidence suggesting that the efficiency of one of the molecular mechanisms for the cellular uptake of vitamin C declines with age (208). Because maximizing blood concentrations of vitamin C may be important in protecting against oxidative damage to cells and biological molecules, a vitamin C intake of at least 400 mg daily might benefit older adults who are at higher risk for chronic diseases caused, in part, by oxidative damage, such as heart disease, stroke, certain cancers, and cataract.

For more information on the difference between Dr Linus Pauling's recommendation and the Linus Pauling Institute's recommendation for vitamin C intake, select the highlighted text.

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Supplemental Forms

Español

The Bioavailability of Different Forms of Vitamin C (Ascorbic Acid)

In the rapidly expanding market of dietary supplements, it is possible to find vitamin C in many different forms with many claims regarding its efficacy or bioavailability. Bioavailability refers to the degree to which a nutrient (or drug) becomes available to the target tissue after it has been administered. We reviewed the literature for the results of scientific research on the bioavailability of different forms of vitamin C.

Natural vs. synthetic ascorbic acid

Natural and synthetic L-ascorbic acid are chemically identical, and there are no known differences in their biological activity. The possibility that the bioavailability of L-ascorbic acid from natural sources might differ from that of synthetic ascorbic acid was investigated in at least two human studies, and no clinically significant differences were observed. A study of 12 males (6 smokers and 6 nonsmokers) found the bioavailability of synthetic ascorbic acid (powder administered in water) to be slightly superior to that of orange juice, based on blood levels of ascorbic acid, and not different based on ascorbic acid in leukocytes (white blood cells) (1). A study in 68 male nonsmokers found that ascorbic acid consumed in cooked broccoli, orange juice, orange slices, and as synthetic ascorbic acid tablets are equally bioavailable, as measured by plasma ascorbic acid levels (2, 3).

Different forms of ascorbic acid

The gastrointestinal absorption of ascorbic acid occurs through an active transport process, as well as through passive diffusion. At low gastrointestinal concentrations of ascorbic acid active transport predominates, while at high gastrointestinal concentrations active transport becomes saturated, leaving only passive diffusion. In theory, slowing down the rate of stomach emptying (e.g., by taking ascorbic acid with food or taking a slow-release form of ascorbic acid) should increase its absorption. While the bioavailability of ascorbic acid appears equivalent whether it is in the form of powder, chewable tablets, or non-chewable tablets, the bioavailability of ascorbic acid from slow-release preparations is less certain.

A study of three men and one woman found 1 gram of ascorbic acid to be equally well absorbed from solution, tablets, and chewable tablets, but the absorption from a timed-release capsule was 50% lower. Absorption was assessed by measuring urinary excretion of ascorbic acid after an intravenous dose of ascorbic acid and then comparing it to urinary excretion after the oral dosage forms (4).

A more recent study examined the plasma levels of ascorbic acid in 59 male smokers supplemented for two months with either 500 mg/day of slow-release ascorbic acid, 500 mg/day of plain ascorbic acid, or a placebo. After two months of supplementation no significant differences in plasma ascorbic acid levels between the slow-release and plain ascorbic acid groups were found (5). A second placebo-controlled trial also evaluated plain ascorbic acid versus slow-release ascorbic acid in 48 male smokers (6). Participants were supplemented with either 250 mg plain ascorbic acid, 250 mg slow-release ascorbic acid, or placebo twice daily for four weeks. No differences were observed in the change in plasma ascorbate concentration or area under the curve following ingestion of either formulation.

Mineral ascorbates

Mineral salts of ascorbic acid (mineral ascorbates) are less acidic, and therefore, considered "buffered." Thus, mineral ascorbates are often recommended to people who experience gastrointestinal problems (upset stomach or diarrhea) with plain ascorbic acid. There appears to be little scientific research to support or refute the claim that mineral ascorbates are less irritating to the gastrointestinal tract. When mineral salts of ascorbic acid are taken, both the ascorbic acid and the mineral appear to be well absorbed, so it is important to consider the dose of the mineral accompanying the ascorbic acid when taking large doses of mineral ascorbates. For the following discussion, it should be noted that 1 gram (g)= 1,000 milligrams (mg) and 1 milligram (mg) = 1,000 micrograms (µg). Mineral ascorbates are available in the following forms:

- **Sodium ascorbate:** 1,000 mg of sodium ascorbate generally contains 111 mg of sodium. Individuals following low-sodium diets (e.g., for high blood pressure) are generally advised to keep their total dietary sodium intake to less than 2,500 mg/day. Thus, megadoses of vitamin C in the form of sodium ascorbate could significantly increase sodium intake (see Sodium Chloride).
- **Calcium ascorbate:** Calcium ascorbate generally provides 90-110 mg of calcium (890-910 mg of ascorbic acid) per 1,000 mg of calcium ascorbate. Calcium in this form appears to be reasonably well absorbed. The recommended dietary calcium intake for adults is 1,000 to 1,200 mg/day. Total calcium intake should not exceed the UL, which is 2,500 mg/day for adults aged 19-50 years and 2,000 mg/day for adults older than 50 years (see Calcium).

The following mineral ascorbates are more likely to be found in combination with other mineral ascorbates, as well as other minerals. It's a good idea to check the labels of dietary supplements for the ascorbic acid dose as well as the dose of each mineral. Recommended dietary intakes and maximum upper levels of intake (when available) are listed after the individual mineral ascorbates below:

- **Potassium ascorbate:** The minimal requirement for potassium is thought to be between 1.6 and 2.0 g/day. Fruit and vegetables are rich sources of potassium, and a diet rich in fruit and vegetables may provide as much as 8 to 11 g/day. Acute and potentially fatal potassium toxicity (hyperkalemia) is thought to occur at a daily intake of about 18 g/day of potassium in adults. Individuals taking potassium-sparing diuretics and those with renal insufficiency (kidney failure) should avoid significant intake of potassium ascorbate. The purest form of commercially available potassium ascorbate contains 0.175 grams (175 mg) of potassium per gram of ascorbate (see Potassium).
- **Magnesium ascorbate:** The recommended dietary allowance (RDA) for magnesium is 400-420 mg/day for adult men and 310-320 mg/day for adult women. The upper level (UL) of intake for magnesium from supplements should not exceed 350 mg/day (see Magnesium).
- **Zinc ascorbate:** The RDA for zinc is 11 mg/day for adult men and 8 mg/day for adult women. The upper level (UL) of zinc intake for adults should not exceed 40 mg/day (see Zinc).
- **Molybdenum ascorbate:** The RDA for molybdenum is 45 micrograms (µg)/day for adult men and women. The upper level (UL) of molybdenum intake for adults should not exceed 2,000 µg (2 mg)/day (see Molybdenum).
- **Chromium ascorbate:** The recommended dietary intake (AI) for chromium is 30-35 µg/day for adult men and 20-25 µg/day for adult women. A maximum upper level (UL) of intake has not been determined by the US Food and Nutrition Board (see Chromium).
- **Manganese ascorbate:** The recommended dietary intake (AI) for manganese is 2.3 mg/day for adult men and 1.8 mg/day for adult women. The upper level (UL) of intake for manganese for adults should not exceed 11 mg/day. Manganese ascorbate is found in some preparations of glucosamine and chondroitin sulfate, and following the recommended dose on the label of such supplements could result in a daily intake exceeding the upper level for manganese (see Manganese).

Vitamin C with bioflavonoids

Bioflavonoids or flavonoids are polyphenolic compounds found in plants. Vitamin C-rich fruit and vegetables, especially citrus fruit, are often rich sources of flavonoids as well. The effect of bioflavonoids on the bioavailability of ascorbic acid has been recently reviewed (7).

Results from the 10 clinical studies comparing the absorption of vitamin C alone or vitamin C in flavonoid-containing foods showed no appreciable differences in bioavailability of ascorbic acid. Only one study, which included five men and three women, found that a 500-mg supplement of synthetic ascorbic acid, given in a natural citrus extract containing bioflavonoids, proteins, and carbohydrates, was more slowly absorbed and 35% more bioavailable than synthetic ascorbic acid alone, when based on plasma levels of ascorbic acid (8). The remaining studies showed either no change or slightly lower plasma ascorbate levels in subjects who consumed vitamin C with flavonoids compared to flavonoids alone (7).

Another assessment of vitamin C bioavailability is measuring urinary ascorbate levels to approximate rates of vitamin C excretion. One study in six young Japanese males (22-26 years old) showed a significant reduction in urinary excretion of ascorbic acid in the presence of acerola juice, a natural source of both vitamin C and flavonoids (9). However, three separate studies showed that urinary levels of vitamin C were increased after consumption of kiwifruit (10), blackcurrant juice (11), or orange juice (1). Overall, the impact of flavonoids on the bioavailability of vitamin C seems to be negligible; however, there is a need for carefully controlled studies using specific flavonoid extracts (7).

Ascorbate and vitamin C metabolites (Ester-C®)

Ester-C® contains mainly calcium ascorbate, but also contains small amounts of the vitamin C metabolites, dehydroascorbic acid (oxidized ascorbic acid), calcium threonate, and trace levels of xylonate and lyxonate. In their literature, the manufacturers state that the metabolites, especially threonate, increase the bioavailability of the vitamin C in this product, and they indicate that they have performed a study in humans that demonstrates the increased bioavailability of vitamin C in Ester-C®. This study has not been published in a peer-reviewed journal. A small published study of vitamin C bioavailability in eight women and one man found no difference between Ester-C® and commercially available ascorbic acid tablets with respect to the absorption and urinary excretion of vitamin C (12). Ester-C® should not be confused with ascorbyl palmitate, which is also marketed as "vitamin C ester" (see below).

Ascorbyl palmitate

Ascorbyl palmitate is a fat-soluble antioxidant used to increase the shelf life of vegetable oils and potato chips (13). It is an amphipathic molecule, meaning one end is water-soluble and the other end is fat-soluble. This dual solubility allows it to be incorporated into cell membranes. When incorporated into the cell membranes of human red blood cells, ascorbyl palmitate has been found to protect them from oxidative damage and to protect α-tocopherol (a fat-soluble antioxidant) from oxidation by free radicals (14). However, the protective effects of ascorbyl palmitate on cell membranes have only been demonstrated in the test tube. Taking ascorbyl palmitate orally probably doesn't result in any significant incorporation into cell membranes because most of it appears to be hydrolyzed (broken apart into palmitate and ascorbic acid) in the human digestive tract before it is absorbed. The ascorbic acid released by the hydrolysis of ascorbyl palmitate appears to be as bioavailable as ascorbic acid alone (15). The presence of ascorbyl palmitate in oral supplements contributes to the ascorbic acid content of the supplement and probably helps protect fat-soluble antioxidants in the supplement. The roles of vitamin C in promoting collagen synthesis and as an antioxidant have generated interest in its use on the skin (see the article, Vitamin C and Skin Health). Ascorbyl palmitate is frequently used in topical preparations because it is more stable than some aqueous (water-soluble) forms of vitamin C (16). Ascorbyl palmitate is also marketed as vitamin C ester," which should not be confused with Ester-C® (see above).

D-Isoascorbic acid (Erythorbic acid)

Erythorbic acid is an isomer of ascorbic acid. Isomers are compounds that have the same kinds and numbers of atoms, but different molecular arrangements. The difference in molecular arrangement among isomers may result in different chemical properties. Erythorbic acid is used in the US as an antioxidant food additive and is generally recognized as safe. It has been estimated that more than 200 mg erythorbic acid per capita is introduced daily into the US food system. Unlike ascorbic acid, erythorbic acid does not appear to exert vitamin C activity, for example, it did not prevent scurvy in guinea pigs (one of the few animal species other than humans that does not synthesize ascorbic acid). However, guinea pig studies also indicated that increased erythorbic acid intake reduced the bioavailability of ascorbic acid by up to 50%. In contrast, a series of studies in young women found that up to 1,000 mg/day of erythorbic acid for as long as 40 days was rapidly cleared from the body and had little effect on the bioavailability of ascorbic acid, indicating that erythorbic acid does not diminish the bioavailability of ascorbic acid in humans at nutritionally relevant levels of intake (17).

Other formulations of vitamin C

PureWay-C® is composed of vitamin C and lipid metabolites. Two cell culture studies using PureWay-C® have been published by the same investigators (18, 19), but *in vivo* data are currently lacking. A small study in healthy adults found that serum levels of vitamin C did not differ when a single oral dose (1 gram) of either PureWay-C® or ascorbic acid was administered (20).

Another formulation of vitamin C, liposomal-encapsulated vitamin C (e.g., Lypo-spheric™ vitamin C) is now commercially available. One report suggested that liposomal-encapsulated vitamin C may be better absorbed than the vitamin in a non-encapsulated form (21).

Large-scale, pharmacokinetic studies are needed to determine how the bioavailability of these vitamin C formulations compares to that of ascorbic acid.

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Pauling Recommendation

Difference Between Dr. Linus Pauling's Recommendations and the LPI's Recommendation for Vitamin C Intake

Dr. Pauling, for whom the Linus Pauling Institute has great respect, based his own recommendations for vitamin C largely on theoretical arguments. In developing his recommendations, he used cross-species comparisons, evolutionary arguments, the concept of biochemical individuality, and the amount of vitamin C likely consumed in a raw plant food diet. Using this approach, Dr. Pauling suggested in the early 1970s that the optimum daily intake may be about 2,000 milligrams of vitamin C and that everyone should get at least 200 to 250 mg/day. In a 1974 radio interview, he noted that "the first 250 mg is more important than any later 250 mg. The first 250 mg leads you up to the level where the blood is saturated. You can achieve a higher volume [concentration] in the blood by a larger intake, but you get much better improvement for the first 250 mg than for additional grams." Dr. Pauling significantly increased his recommendation in his 1986 book *How To Live Longer and Feel Better*. At the Linus Pauling Institute, we have based our vitamin C recommendations on the current body of scientific evidence, which is significantly greater than it was at Pauling's time but remains incomplete owing to the many diverse functions of vitamin C in the human body that have yet to be fully understood.

In this context, it is important to note that data from the National Institutes of Health (NIH) have indicated that vitamin C levels in plasma and circulating cells become fully saturated at intakes of about 400 mg/day in young, healthy nonsmokers. These observations are consistent with other data that intakes of about 400 mg/day are associated with reduced risk of heart disease. While these NIH studies are the best we currently have regarding the pharmacokinetics of vitamin C in the human body, they have numerous limitations, including the fact that they are based on a small number of young, healthy men and women. We currently do not know how much vitamin C is required to achieve saturation of cells and tissues in children, older adults, and diseased or stressed individuals. A meta-analysis of 36 studies on the relationship between vitamin C intake and plasma concentrations found that the elderly require a substantially higher daily intake of vitamin C to attain plasma concentrations that younger adults achieve at a lower intake. Additionally, work by Linus Pauling Institute investigators has shown that cellular uptake of vitamin C declines with age, supporting the notion that vitamin C requirements are increased in the elderly.

Therefore, the Linus Pauling Institute's intake recommendation of 400 mg/day of vitamin C for generally healthy adults takes into account the currently available epidemiological, biochemical, and clinical evidence, while acknowledging the extremely low toxicity of vitamin C and the incomplete information regarding optimum intake. It should also be noted that the Linus Pauling Institute's recommendation is strictly directed towards prevention of disease in healthy individuals, not treatment of disease. Thus, individuals suffering from certain diseases may require substantially larger amounts of vitamin C to achieve optimum body levels or derive therapeutic benefits, areas that were of great interest to Linus Pauling and need to be further explored.

Vitamin D

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Summary

- Vitamin D can be synthesized in the skin upon exposure to sunlight and is then metabolized in the liver and kidney to the metabolically active form called 1α,25-dihydroxyvitamin D. Through binding to the vitamin D receptor (VDR), 1α,25-dihydroxyvitamin D can regulate the expression of hundreds of genes involved in skeletal and other biological functions. *(More information)*
- Vitamin D is essential for maintenance of bone mineralization through the regulation of calcium and phosphorus homeostasis. Vitamin D also exhibits many non-skeletal effects, particularly on the immune, endocrine, and cardiovascular systems. *(More information)*
- Vitamin D is important for normal bone development and maintenance. Severe vitamin D deficiency causes rickets in children and osteomalacia in adults. *(More information)*
- Secondary hyperparathyroidism due to vitamin D insufficiency can increase bone breakdown and precipitate osteoporosis. Randomized clinical trials indicate that supplementation with at least 800 IU/day of vitamin D may reduce the risk of falls and fractures in older individuals. *(More information)*
- Vitamin D can regulate cell differentiation and growth by binding to the vitamin D receptor found in most body cells. Observational studies have reported associations between low sun exposure, poor vitamin D status, and increased risk of developing colorectal and breast cancer. Randomized controlled trials are needed to evaluate whether cancer prevention may benefit from vitamin D supplementation. *(More information)*
- Various observational studies have reported inverse associations between vitamin D status and the susceptibility or severity of autoimmune diseases, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. *(More information)*
- Current evidence from observational studies suggests an inverse relationship between circulating vitamin D concentrations and risk of type 2 diabetes mellitus. It is not yet known whether correcting vitamin D deficiency in individuals with glucose intolerance can decrease the risk of progression to type 2 diabetes mellitus. *(More information)*
- Randomized clinical trials are currently investigating whether vitamin D supplementation can limit cognitive deterioration and disease progression in subjects with neurodegenerative disease. *(More information)*
- Vitamin D insufficiency in pregnant women may be associated with several adverse effects for the mother and newborn. Safety and benefits of vitamin D supplementation during pregnancy both need to be evaluated in clinical trials. *(More information)*
- Observational studies have documented an association between vitamin D deficiency and increased incidence and severity of the coronavirus disease, COVID-19. *(More information)*
- Preliminary studies have shown that vitamin D supplementation may offer promising improvements in the management of atopic dermatitis (eczema) and Crohn's disease. *(More information)*

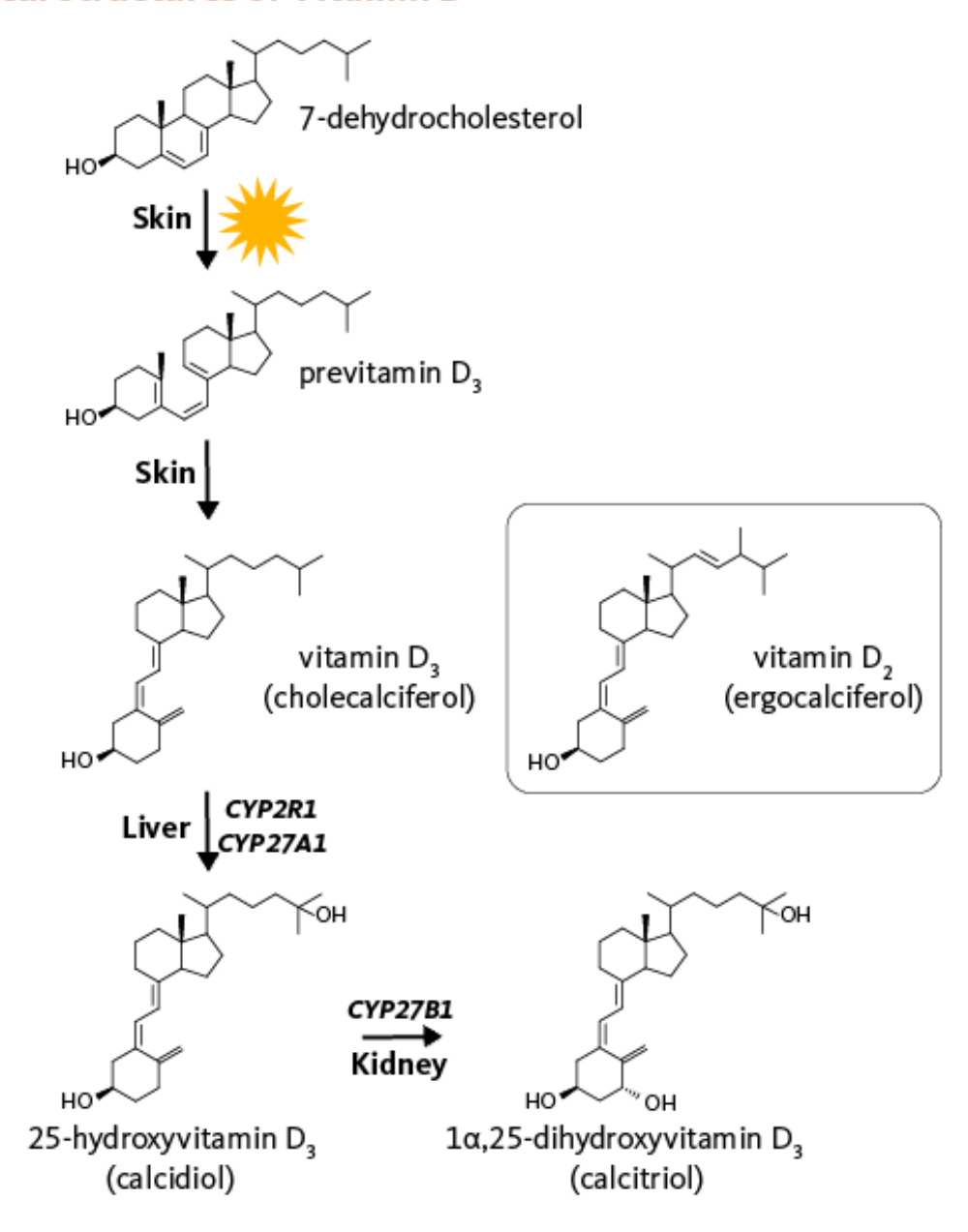
Vitamin D is a fat-soluble vitamin that regulates calcium homeostasis and is vital for bone health (1). While it can also be obtained from dietary sources or supplements, vitamin D$_3$ (cholecalciferol) is synthesized in the human skin from 7-dehydrocholesterol upon exposure to ultraviolet-B (UVB) radiation from sunlight (see the separate article on Vitamin D and Skin Health). Vitamin D$_2$ (ergocalciferol) is a vitamin D analog photosynthesized in plants, mushrooms, and yeasts; vitamin D$_2$ is also sometimes used in vitamin D food fortification (2). When vitamin D$_3$ in skin is inadequate due to insufficient exposure to UVB radiation, oral intake of vitamin D is necessary to meet vitamin D requirements.

Function

Vitamin D metabolism

Cholecalciferol and ergocalciferol are biologically inactive precursors of vitamin D and must be converted to biologically active forms in the liver and kidneys (**Figure 1**). Indeed, following dietary intake or synthesis in the epidermis of skin after UVB exposure, both forms of vitamin D enter the circulation and are transported to the liver by the vitamin D-binding protein (and to a lesser extent by albumin). In hepatocytes (liver cells), vitamin D is hydroxylated to form 25-hydroxyvitamin D (calcidiol; calcifediol). Exposure to sunlight or dietary intake of vitamin D increases serum concentrations of 25-hydroxyvitamin D. 25-Hydroxyvitamin D constitutes the major circulating form of vitamin D, and the sum of 25-hydroxyvitamin D$_2$ and 25-hydroxyvitamin D$_3$ concentrations in serum is used as an indicator of vitamin D nutritional status (3). The renal 25-hydroxyvitamin D$_3$-1α-hydroxylase enzyme (also known as CYP27B1) eventually catalyzes a second hydroxylation that converts 25-hydroxyvitamin D to 1α,25-dihydroxyvitamin D (calcitriol). The production of 1α,25-dihydroxyvitamin D in the kidneys is regulated by several factors, including serum phosphorus, calcium, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and 1α,25-dihydroxyvitamin D itself. While the kidney is the main source of 1α-hydroxylase activity, extra-renal production of 1α,25-dihydroxyvitamin D has also been demonstrated in a variety of tissues, including skin, parathyroid gland, breast, colon, prostate, as well as cells of the immune system and bone cells (2). Most of the physiological effects of vitamin D in the body are related to the activity of 1α,25-dihydroxyvitamin D (4). Various forms of vitamin D are listed in **Figure 1**.

Figure 1. Chemical Structures of Vitamin D


7-dehydrocholesterol
Skin
vitamin D$_3$ (cholecalciferol)
vitamin D$_2$ (ergocalciferol)
Liver
CYP2R1
CYP27A1
CYP27B1
Kidney
25-hydroxyvitamin D$_3$ (calcidiol)
1α,25-dihydroxyvitamin D$_3$ (calcitriol)
HO
OH

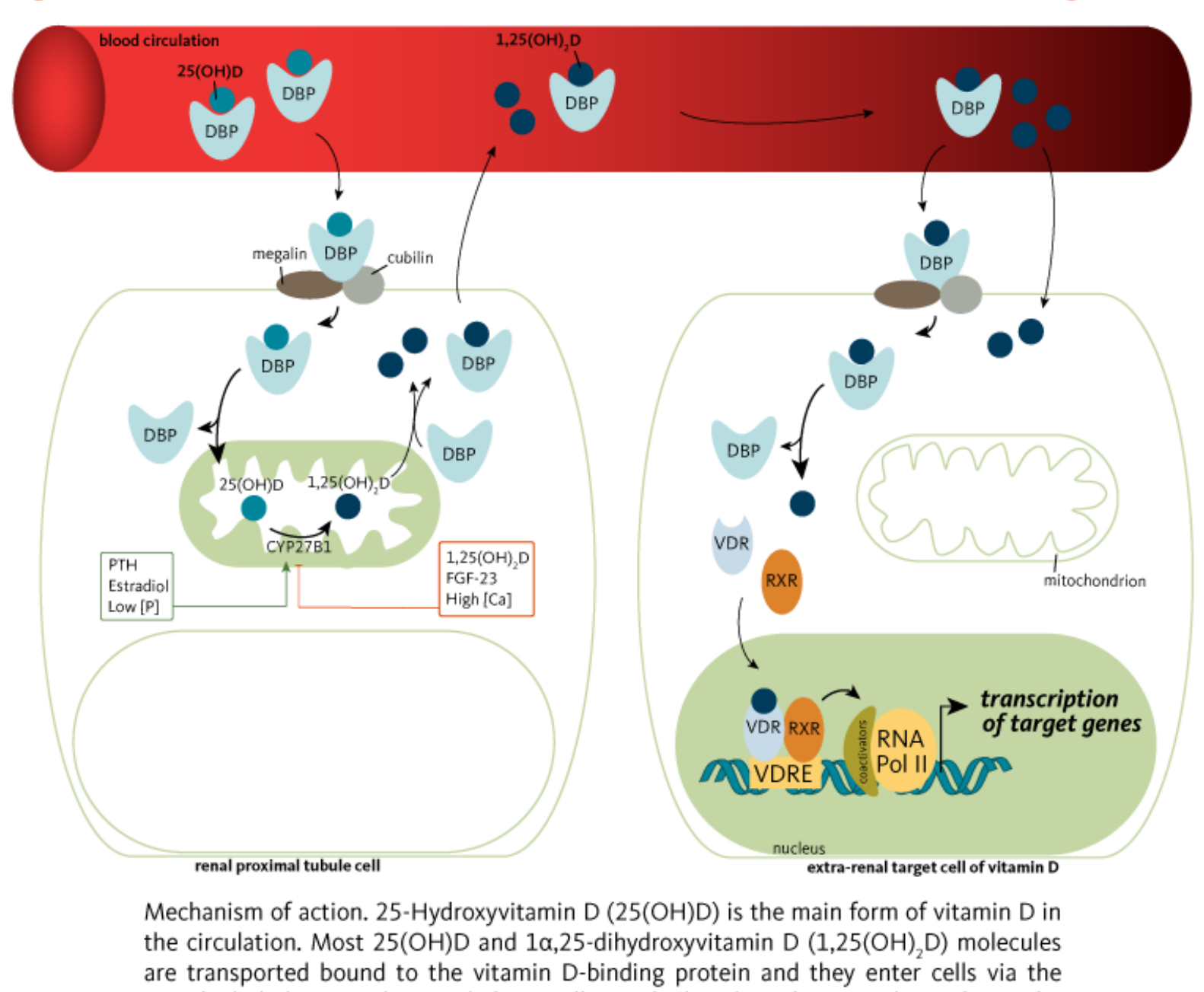
Vitamin D synthesis. Previtamin D$_3$ is synthesized in the upper layers of the skin from 7-dehydrocholesterol by the action of ultraviolet light (UVB). A nonenzymatic conversion of previtamin D$_3$ into vitamin D$_3$ (cholecalciferol) then occurs in lower layers of the skin. Vitamin D$_3$ is quickly transported to adipose tissue for storage or liver for activation. In liver cells, several cytochrome P450 (CYP) enzymes can catalyze the 25-hydroxylation of vitamin D$_3$ (or plant-based vitamin D$_2$ or ergocalciferol). The product of this step, 25-hydroxyvitamin D$_3$, is converted into the active form of vitamin D$_3$, 1α,25-dihydroxyvitamin D, in a reaction catalyzed by CYP27B1. This 1α-hydroxylation takes place primarily in the kidney.

[Figure 1 - Click to Enlarge]

Mechanisms of action

Most, if not all, actions of vitamin D are mediated through a nuclear transcription factor known as the vitamin D receptor (VDR) (**Figure 2**) (5). Upon entering the nucleus of a cell, 1α,25-dihydroxyvitamin D binds to the VDR and recruits another nuclear receptor known as retinoid X receptor (RXR). In the presence of 1α,25-dihydroxyvitamin D, the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes. Thousands of VDREs have been identified throughout the genome, and VDR activation by 1α,25-dihydroxyvitamin D is thought to directly and/or indirectly regulate 100 to 1,250 genes (6).

Figure 2. Conversion to the Active Form of Vitamin D and VDR-mediated Gene Regulation



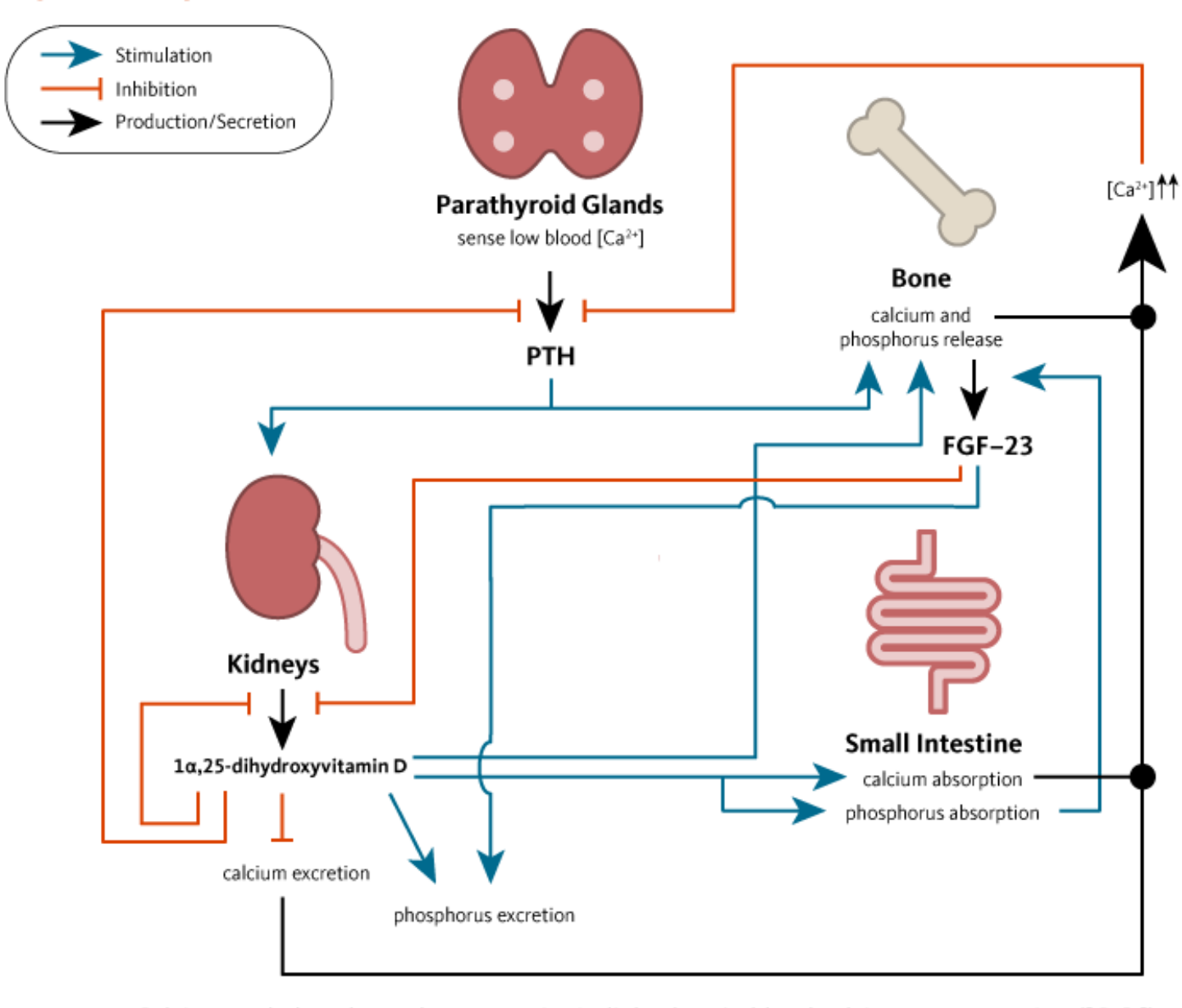
Mechanism of action. 25-Hydroxyvitamin D (25(OH)D) is the main form of vitamin D in the circulation. Most 25(OH)D and 1α,25-dihydroxyvitamin D (1,25(OH)$_2$D) molecules are transported bound to the vitamin D-binding protein and they enter cells via the megalin/tubulin complex. In kidney cells, 1α-hydroxylase (CYP27B1) catalyzes the conversion of 25(OH)D into 1,25(OH)$_2$D. Parathyroid hormone (PTH), estradiol, and low phosphorus concentration ([P]) stimulate this reaction, whereas 1,25(OH)$_2$D, fibroblast growth factor-23 (FGF-23), and high calcium concentration ([Ca]) inhibit it. 1,25(OH)$_2$D enters the circulation and is transported to extra-renal target tissues where it can regulate gene expression. In the nucleus of target cells, 1,25(OH)$_2$D binds to the vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor (RXR). VDR-RXR binds to vitamin D response elements (VDRE) in the promoter of vitamin D target genes. *25(OH)D, 25-hydroxyvitamin D; 1,25(OH)$_2$D, 1α,25-dihydroxyvitamin D; [Ca], calcium concentration; CYP2R1, 1α-hydroxylase; DBP, vitamin D-binding protein; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone; [P], phosphorus concentration; RNA Pol II, RNA polymerase II; RXR, retinoid X receptor; VDR, vitamin D nuclear receptor; VDRE, vitamin D response element.*

[Figure 2 - Click to Enlarge]

Calcium balance

Maintenance of serum calcium concentrations within a narrow range is vital for normal functioning of the nervous system, as well as for bone growth and maintenance of bone density. Vitamin D is essential for the efficient utilization of calcium by the body (1). The parathyroid glands sense serum calcium concentrations and secrete parathyroid hormone (PTH) if calcium concentrations decrease below normal (**Figure 3**). Elevations in PTH stimulate the activity of the 25-hydroxyvitamin D$_3$-1α-hydroxylase enzyme in the kidney, resulting in the increased production of 1α,25-dihydroxyvitamin D. The active vitamin D form, 1α,25-dihydroxyvitamin D, is released into the circulation and transported to target tissues. Within target cells, 1α,25-dihydroxyvitamin D binds to and induces the activation of VDR, which leads to changes in gene expression that normalize serum calcium by (1) increasing the intestinal absorption of dietary calcium, (2) increasing the reabsorption of calcium filtered by the kidneys, and (3) mobilizing calcium from bone when there is insufficient dietary calcium to maintain normal serum calcium concentrations (7).

Figure 3. Regulation of Calcium and Phosphorus Homeostasis



Calcium and phosphorus homeostasis. A slight drop in blood calcium concentration ([Ca^{2+}]) results in the secretion of parathyroid hormone (PTH) by the parathyroid glands. PTH simulates the activity of CYP27B1 (25-hydroxyvitamin D-1α-hydroxylase enzyme) that catalyzes the hydroxylation of 25-hydroxyvitamin D into 1α,25-dihydroxyvitamin D. This active form of vitamin D (i) increases the reabsorption of calcium filtered by the kidneys and stimulates phosphorus excretion, (ii) increases the intestinal absorption of both calcium and phosphorus, and (iii) mobilizes calcium (and phosphorus) from bone when dietary calcium intake is insufficient. PTH also stimulates bone resorption that releases calcium and phosphorus. 1α,25-dihydroxyvitamin D inhibits its own production, as well as PTH synthesis, via negative feedback loops. FGF-23 is secreted by bone-forming cells (osteoblasts) in response to an increase in phosphorus intake. FGF-23 inhibits the synthesis of 1α,25-dihydroxyvitamin D and promotes phosphorus excretion in the urine.
[Ca^{2+}], calcium concentration; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

[Figure 3 - Click to Enlarge]

Phosphorus balance

The regulations of calcium and phosphorus homeostasis are closely related, and the calciotropic hormones, PTH and 1α,25-dihydroxyvitamin D, can also control serum phosphorus. Specifically, 1α,25-dihydroxyvitamin D increases intestinal phosphorus absorption by stimulating the expression of a sodium-phosphate cotransporter in the small intestine. While PTH increases urinary excretion of phosphorus by reducing reabsorption in the kidney, it is not yet clear whether 1α,25-dihydroxyvitamin D can directly regulate renal phosphorus transport. The phosphaturic hormone fibroblast growth factor-23 (FGF-23), secreted by osteoblasts (bone-forming cells), limits the production of 1α,25-dihydroxyvitamin D by inhibiting 25-hydroxyvitamin D-1α-hydroxylase (**Figure 3**) (reviewed in 8).

Cell differentiation

Cells that are dividing rapidly are said to be proliferating. Differentiation results in the specialization of cells for specific functions. In general, differentiation of cells leads to a decrease in proliferation. While cellular proliferation is essential for growth and wound healing, uncontrolled proliferation of cells with certain mutations may lead to cancer. The active form of vitamin D, 1α,25-dihydroxyvitamin D, inhibits proliferation and stimulates the differentiation of cells through binding to the VDR (1).

Immunity

Acting through the VDR, 1α,25-dihydroxyvitamin D is a potent immune system modulator. The VDR is expressed by most cells of the immune system, including regulatory T cells and antigen-presenting cells, such as dendritic cells and macrophages (9). Under specific circumstances, monocytes, macrophages, and T cells can express the 25-hydroxyvitamin D$_3$-1α-hydroxylase enzyme and produce 1α,25-dihydroxyvitamin D, which acts locally to regulate the immune response (10, 11). There is considerable scientific evidence that 1α,25-dihydroxyvitamin D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmunity (12). Conversely, vitamin D deficiency may compromise the integrity of the immune system and lead to inappropriate immune responses (see Autoimmune diseases).

Insulin secretion

The VDR is expressed by insulin-secreting cells of the pancreas, and the results of animal studies suggest that 1α,25-dihydroxyvitamin D plays a role in insulin secretion under conditions of increased insulin demand (13, 14). Cross-sectional and prospective studies suggest that insufficient vitamin D status may have an adverse effect on insulin secretion and glucose tolerance in type 2 diabetes mellitus (noninsulin-dependent diabetes mellitus) (reviewed in 15).

Blood pressure regulation

The renin-angiotensin system plays an important role in the regulation of blood pressure (16). Renin is an enzyme that catalyzes the cleavage (splitting) of a small peptide (angiotensin I) from a larger protein (angiotensinogen) produced in the liver. Angiotensin-converting enzyme (ACE) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing sodium and water retention. The rate of angiotensin II synthesis is dependent on renin (17). Research in mice lacking the gene encoding the VDR indicates that 1α,25-dihydroxyvitamin D decreases the expression of the gene encoding renin through its interaction with the VDR (18). Since inappropriate activation of the renin-angiotensin system can contribute to the development of hypertension, achieving adequate vitamin D status may be important for decreasing the risk of high blood pressure (see Hypertension).

Deficiency

In vitamin D deficiency, calcium absorption cannot be increased enough to satisfy the body's calcium needs (4). Consequently, PTH production by the parathyroid glands is increased and calcium is mobilized from the skeleton to maintain normal serum calcium concentrations — a condition known as secondary hyperparathyroidism. Although it has long been known that severe vitamin D deficiency has serious consequences for bone health, research suggests that less obvious states of vitamin D deficiency are common and increase the risk of osteoporosis and various other health problems (see Disease Prevention).

Severe vitamin D deficiency

Rickets

In infants and children, severe vitamin D deficiency results in the failure of bone to mineralize. The process of mineralization, which involves the production of crystals of calcium phosphate by bone-forming cells, determines the hardness and strength of bones. Vitamin D deficiency severely affects rapidly growing bones. The growth plates of bones continue to enlarge, but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. In infants, rickets may result in delayed closure of the fontanels (soft spots) in the skull, and the rib cage may become deformed due to the pulling action of the diaphragm. In severe cases, low serum calcium concentrations (hypocalcemia) may cause seizures. Although fortification of food has led to complacency regarding vitamin D deficiency, nutritional rickets is still being reported throughout the world (19, 20).

Osteomalacia

Although adult bones are no longer growing, they are in a constant state of turnover, or "remodeling." In adults with severe vitamin D deficiency, the collagenous bone matrix is preserved, but bone mineral is progressively lost, resulting in a softening of bones (osteomalacia), bone pain, and increased risk of osteoporosis (21).

Muscle weakness and pain

Vitamin D deficiency causes muscle weakness and pain in children and adults. Muscle pain and weakness were prominent symptoms of vitamin D deficiency in a study of Arab and Danish Muslim women living in Denmark (22). In a cross-sectional study of 150 consecutive patients referred to a clinic in Minnesota for the evaluation of persistent, nonspecific musculoskeletal pain, 93% had serum 25-hydroxyvitamin D concentrations equal to or below 20 ng/mL, with a mean concentration of 12.1 ng/mL, which is indicative of vitamin D insufficiency (23). Loss of muscle strength greatly contributes to increased risk of falling and bone fractures, especially in older people (24). In addition, long-term vitamin D insufficiency may be a contributing factor to osteoporosis in the elderly (see Osteoporosis).

Risk factors for vitamin D deficiency

Both environmental factors and cultural practices result in variations in vitamin D status:

- Environmental conditions: Geographical locations, including latitude and altitudes, and atmospheric conditions (e.g., air pollution, presence of clouds) greatly influence the intensity of UVB radiation that reaches the ground. Seasonal changes also affect the quality and quantity of UVB rays and thus vitamin D production in skin (25-27).
- Concealed clothing style: In a study of 2,032 Middle Eastern women, who wore a headscarf or covered all skin for religious or cultural reasons, 96% had serum 25-hydroxyvitamin D concentrations less than 20 ng/mL, and 60% had vitamin D concentrations below 12 ng/mL (28). Rickets and osteomalacia are not uncommon in the Middle East and North African regions where children and women cover the majority or all of their skin whenever outside (29).
- Sun safety measures: Sun protection practices, including limiting sun exposure, wearing protective clothing and hats, and applying sunscreens, hinder skin exposure to sunlight and thus result in lower vitamin D$_3$ production and circulating vitamin D metabolites unless there is adequate oral intake. Of note, the application of sunscreen (2 mg/cm^2) with a sun protection factor (SPF) of 10 reduces UVB radiation by 90% (30).
- Exclusively breast-fed infants: Infants who are exclusively breast-fed and do not receive vitamin D supplementation are at high risk for vitamin D deficiency, particularly if they have dark skin and/or receive little sun exposure (19). Human milk generally provides 10 to 80 IU of vitamin D per liter (L), which corresponds to 0.2 to 1.5 g/day (8 to 60 IU/day) when using an average daily milk intake of 0.75 L (25 oz) (31). The American Academy of Pediatrics recommends that all breast-fed and partially breast-fed infants be given an oral vitamin D supplement of 400 IU/day (19). Maternal vitamin D supplementation during breast-feeding may contribute to improved vitamin D status of the breast-fed infant, especially in populations with a high prevalence of vitamin D deficiency (32). Older infants and toddlers exclusively fed milk substitutes (e.g., soy-based formulas) and weaning foods that are not vitamin D fortified are at risk for vitamin D deficiency (33).

The efficiency of vitamin D synthesis, absorption, and metabolism also depends on a variety of biological factors:

- Skin pigmentation: People with a dark complexion synthesize less vitamin D on exposure to sunlight than those with light-colored skin (34). A national US survey reported average serum 25-hydroxyvitamin D concentrations of 28.1 ng/mL, 21.6 ng/mL, and 16.9 ng/mL in Caucasian, Mexican American, and African American adults aged ≥20 years old, respectively (25).
- Genetic variations: An international, multicenter, genome-wide association study (GWAS) of 15 cohorts, including ~30,000 participants of European descent — known as the SUNLIGHT [Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits] consortium — identified common variations (called polymorphisms) in genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport that influence vitamin D status (35). While genetic determinants of low vitamin D status are being identified in populations of European (36, 37) and Asian descent (38, 39), genome-wide association studies are needed in populations of African descent.
- Older age: The elderly have reduced capacity to synthesize vitamin D in skin when exposed to UVB radiation and are more likely to stay indoors or use sunscreen, which prevents vitamin D synthesis. It has been estimated that across Canada, the US, and Europe, the prevalence of vitamin D deficiency ranges between 20%-100% in free-living elderly (40). Moreover, institutionalized adults who are not supplemented with vitamin D are at extremely high risk of vitamin D deficiency (41, 42).
- Chronic kidney disease (CKD): Vitamin D deficiency in patients with impaired renal function is due to a reduced synthesis of 1α,25-dihydroxyvitamin D and an increased loss of 25-hydroxyvitamin D in urine (43).
- Fat malabsorption syndromes: Vitamin D deficiency is common among people with cystic fibrosis and both cholestatic and non-cholestatic liver diseases due to decreased absorption of dietary vitamin D and impaired conversion of vitamin D to 25-hydroxyvitamin D (reviewed in 44).
- Inflammatory bowel disease: People with inflammatory bowel disease like Crohn's disease appear to be at increased risk of vitamin D deficiency, especially those who have had small bowel resections (45).
- Obesity: Obesity (body mass index ≥30 kg/m^2) increases the risk of vitamin D deficiency (46). Once vitamin D is synthesized in the skin or ingested, it can be sequestered in body fat stores, making it less bioavailable to people with higher body fat mass. Moreover, vitamin D supplementation trials have shown that obese people reached much lower serum 25-hydroxyvitamin D concentrations compared to normal weight (BMI <25 kg/m^2) participants with equivalent oral dosages (47).
- Magnesium deficiency: Recent findings suggest that high magnesium intakes may reduce the risk of vitamin D insufficiency. Magnesium regulates the activity of critical enzymes in vitamin D metabolism, which would explain how magnesium deficiency negatively affects vitamin D status (48).

Assessing vitamin D nutritional status

Growing awareness that vitamin D insufficiency has serious health consequences beyond rickets and osteomalacia highlights the need for accurate assessment of vitamin D nutritional status. It is currently agreed that the measurement of total serum 25-hydroxyvitamin D concentration (1 ng/mL corresponding to 2.5 nmol/L) is the best indicator to evaluate vitamin D status. However, high-quality evidence is still needed to ensure that the current cutoff values are optimal to define states of insufficiency and deficiency (40). Moreover, only recently, efforts have been made toward the standardization of commercially and laboratory-developed 25-hydroxyvitamin D assays, such that guidelines have been developed using largely unstandardized research data (49). Although laboratory reference values for sufficient vitamin D status were initially based on serum 25-hydroxyvitamin D concentrations from cohorts of healthy individuals, additional studies have suggested that health-based cutoff values aimed at preventing secondary hyperparathyroidism and bone loss should be considerably higher. Indeed, while it is considered that serum 25-hydroxyvitamin D concentrations less than 8 to 10 ng/mL (20 to 25 nmol/L) indicate severe deficiency associated with rickets and osteomalacia, several studies have observed that PTH concentrations (50, 51) and calcium absorption (52) were not optimized with serum 25-hydroxyvitamin D concentrations below 32 ng/mL (80 nmol/L).

Yet, more recent studies have failed to find threshold values of serum 25-hydroxyvitamin D concentrations in relation to PTH suppression and optimal calcium absorption. On the one hand, a cross-sectional analysis of 312,962 clinical samples did not find any evidence of threshold for PTH suppression in the well-fitted curve displaying the inverse association between paired measurements of serum PTH and 25-hydroxyvitamin D, even with 25-hydroxyvitamin D concentrations beyond 70 ng/mL (175 nmol/L) (53). This contradicted an analysis of the US National Health and Nutrition Examination Survey (NHANES 2003-2006) that estimated maximum PTH suppression for 25-hydroxyvitamin D concentrations of 40 ng/mL (100 nmol/L) and above (54). In addition, both studies identified evidence of mild hyperparathyroidism (serum PTH >65 pg/mL) in individuals with serum 25-hydroxyvitamin D concentrations well beyond 20 ng/mL (50 nmol/L), questioning the use of serum PTH as a sensible indicator of vitamin D insufficiency (53, 54). On the other hand, a randomized, placebo-controlled trial in postmenopausal women with vitamin D insufficiency (serum 25-hydroxyvitamin D <20 ng/mL) supplemented with daily vitamin D$_3$ doses from 400 to 4,800 IU found little change (6%) in calcium absorption over a normal 25-hydroxyvitamin D concentration range of 20 to 66 ng/mL (55).

The current cutoffs proposed by the Institute of Medicine (IOM) are as follows: deficiency as serum 25-hydroxyvitamin D values <12 ng/mL (<30 nmol/L), insufficiency as serum 25-hydroxyvitamin D values of 12 to 19 ng/mL (30 to 49 nmol/L), and sufficiency as serum 25-hydroxyvitamin D values of 20 to 50 ng/mL (50 to 125 nmol/L) (56). The dietary reference intakes (EAR, RDA) set by the IOM are based on achieving circulating 25-hydroxyvitamin D concentrations (20 to 50 ng/mL) that are adequate to maintain bone health and optimal calcium absorption (57).

Yet, considering the potential role of circulating concentrations lower than 30 ng/mL in the burden of many chronic diseases (6), the US Endocrine Society has suggested to define cutoff values as follows: deficiency as serum 25-hydroxyvitamin D values ≤20 ng/mL (≤50 nmol/L), insufficiency as serum 25-hydroxyvitamin D values of 21 to 29 ng/mL (51 to 74 nmol/L), and sufficiency as serum 25-hydroxyvitamin D values of 30 to 100 ng/mL (75 to 250 nmol/L) (40). This alternate target range is supported by some observational studies, but it is not based on data from randomized controlled trials (see Disease Prevention) (47). With these latter cutoff values, studies from across the world have estimated that hypovitaminosis D is widespread and that children and adults of all ages are equally at risk of insufficiency and deficiency (58). Data from supplementation studies indicate that vitamin D intakes of at least 800 to 1,000 IU/day are required by adults living in temperate latitudes to achieve serum 25-hydroxyvitamin D concentrations of at least 30 ng/mL (75 nmol/L) (40).

Finally, total serum 25-hydroxyvitamin D concentrations may not always adequately reflect vitamin D bioavailability (59), and additional evidence is needed to improve the determination of vitamin D status in different ethnic populations.

The Recommended Dietary Allowance (RDA)

In 2010, the Food and Nutrition Board (FNB) of the IOM set a Recommended Dietary Allowance (RDA) based on the amount of vitamin D needed for bone health. While the RDA was increased from the adequate intake (AI) set in 1997, the optimal levels of recommended intakes and serum 25-hydroxyvitamin D to minimize hyperthyroidism and maximize bone health in the general population remain controversial (40). The RDA for vitamin D is listed in **Table 1** by life stage and gender.

Table 1. Recommended Dietary Allowance (RDA) for Vitamin D

Life Stage	Age	Males		Females	
		µg/day	IU/day	µg/day	IU/day
Infants (AI)	0-6 months	10	400	10	400
Infants (AI)	6-12 months	10	400	10	400
Children	1-3 years	15	600	15	600
Children	4-8 years	15	600	15	600
Children	9-13 years	15	600	15	600
Adolescents	14-18 years	15	600	15	600
Adults	19-70 years	15	600	15	600
Adults	71 years and older	20	800	20	800
Pregnancy	all ages	-	-	15	600
Breast-feeding	all ages	-	-	15	600

Disease Prevention

Mortality

In a nine-year follow-up analysis of the Third US National Health and Nutrition Examination Survey (NHANES III) that included 15,099 participants (of which 77% were Caucasians), serum concentrations of 25-hydroxyvitamin D — standardized as per the methodology developed by the Vitamin D Standardization Program [VDSP] — were examined in relation to mortality. The analysis suggested an increase in all-cause mortality with decreasing serum 25-hydroxyvitamin D concentrations <16 ng/mL (60). In contrast, the risk of all-cause mortality varied little for baseline serum 25-hydroxyvitamin D concentrations in the range of 16 to 40 ng/mL (60). Similar results were obtained in a meta-analysis of eight prospective cohort studies that considered the relationship between standardized 25-hydroxyvitamin D concentrations and mortality during a median follow-up period of 10.5 years. The risk of death was found to be 19% higher with 25-hydroxyvitamin D concentrations between 12 and 15.99 ng/mL and 56% higher with concentrations <12 ng/mL compared to the risk associated with concentrations between 30 and 39.99 ng/mL (61). A meta-analysis of 73 prospective cohort studies, including >800,000 participants, found that the lowest versus highest tertile of serum 25-hydroxyvitamin D concentrations was associated with greater risks of all-cause mortality (+35%), mortality due to cardiovascular disease (+35%), and mortality due to cancer (+14%) (62). Yet, a Mendelian randomization analysis — which limits bias due to confounding and reverse causation (63) — of data from three large Danish cohorts of 95,766 adults found a significant association of genetically low plasma 25-hydroxyvitamin D concentrations with all-cause and cancer-related mortality, but not with cardiovascular disease-related mortality (64). Finally, two meta-analyses of randomized controlled trials have suggested a modest reduction in all-cause mortality in older people supplemented with vitamin D and calcium, but not vitamin D alone (62, 65). Additional placebo-controlled trials need to examine further whether supplementation with vitamin D alone or in combination with calcium might help prevent premature death in replete individuals.

Osteoporosis

Vitamin D status, osteoporosis, and risk of fracture

Although the causes of osteoporosis are multifactorial, vitamin D insufficiency can be an important etiological factor in older adults. Osteoporosis affects one-third of women aged 60 to 70 years and two-thirds of women aged 80 years and above (66). A multinational (18 different countries with latitudes ranging from 64 degrees north to 38 degrees south) survey of more than 2,600 postmenopausal women with osteoporosis revealed that 31% of subjects had 25-hydroxyvitamin D concentrations <20 ng/mL (50 nmol/L) (67). In addition, a case-control study that included 111 hip fracture patients and 73 controls (median age, 83 years) found that lower serum concentrations of both 25-hydroxyvitamin D and vitamin K$_1$ in patients compared to controls were associated with an increased risk of hip fracture (68). Without sufficient vitamin D from sun exposure or dietary intake, intestinal calcium absorption can be significantly reduced. This increases PTH secretion by the parathyroid glands; sustained PTH elevation may result in increased bone resorption, which in turn may increase the risk of osteoporotic fracture (69).

Vitamin D supplementation and bone mineral density

The progressive loss of bone mineral density (BMD) leading to osteopenia (pre-osteoporosis) and osteoporosis is commonly observed in older adults, especially the elderly. The results of a meta-analysis of 23 randomized controlled trials with more than 4,000 participants (mean age, 59 years) showed little evidence for an effect of vitamin D supplementation on BMD at any of the five skeletal sites examined, including lumbar spine, femoral neck, trochanter, forearm, and total body. A significant increase in BMD was reported only at the femoral neck (70). It was, however, suggested that individuals in this age group would have adequate calcium intake and thus normal bone metabolism, explaining the lack of an effect of vitamin D in strengthening bone mass (71). Conversely, in older individuals, vitamin D supplementation is essential to correct and maintain adequate concentrations of serum 25-hydroxyvitamin D and to prevent secondary hyperparathyroidism and BMD loss (72).

Vitamin D supplementation and risk of fracture

A prospective cohort study that followed more than 72,000 postmenopausal women in the US for 18 years found that those who consumed at least 600 IU/day of vitamin D from diet and supplements had a 37% lower risk of osteoporotic hip fracture than women who consumed less than 140 IU/day of vitamin D (73). However, daily supplementation with 400 IU of vitamin D$_3$, in combination with 1,000 mg calcium, did not significantly reduce risk of hip fracture compared to a placebo in 36,282 postmenopausal women from the Women's Health Initiative trial (74), suggesting that there might be a threshold of vitamin D intake that is necessary to observe reductions in fracture risk. Results of a genetic analysis of data from this trial also suggested that beneficial effects of vitamin D and calcium supplementation on fracture risk might be limited to women with the lowest genetic risk of low BMD (75). Yet, this trial has been questioned for reasons that include poor adherence and the fact that participants were allowed to take additional vitamin D and calcium supplements that might have confounded the results. In addition, use of hormone replacement therapy was not considered in the study of the effect of vitamin D and calcium on skeletal health in postmenopausal women despite being a major confounding factor in this population (57, 76).

Another trial, the Randomised Evaluation of Calcium Or vitamin D (RECORD) study, reported that oral supplemental vitamin D$_3$ (800 IU/day) alone, or in combination with calcium (1,000 mg/day), did not prevent the occurrence of osteoporotic fractures in elderly adults who had already experienced a low-trauma, osteoporotic fracture (77). In this latter study as well, a number of limitations, including poor adherence and/or the fact that vitamin D supplementation did not raise serum 25-hydroxyvitamin D concentrations to a level that would protect against fractures, might explain the lack of an effect (78). Despite high adherence to treatment, the incidence of non-vertebral fracture was similar in postmenopausal women supplemented with vitamin D$_3$ (initial dose of 200,000 IU followed by 100,000/month) or placebo for over three years in the Vitamin D Assessment (ViDA) trial (79).

Nevertheless, the US Preventive Services Task Force that conducted the meta-analysis of 11 randomized, placebo-controlled trials, including 52,915 older people (of whom 69% were postmenopausal women), found that the supplementation of vitamin D (300-1,000 IU/day) and calcium (500-1,200 mg/day) for up to seven years resulted in a 12% reduction in the risk of any new fracture (80). Another meta-analysis of 11 randomized, double-blind, placebo-controlled trials on the effect of vitamin D supplementation in 31,022 individuals (91% women) 65 years and older indicated that those with the highest vitamin D intake (792-2,000 IU/day) had a 30% lower risk of hip fracture and a 14% lower risk of any non-spine fracture (81). Finally, a third meta-analysis of trials that examined the effect of combined vitamin D and calcium in preventing fractures in older men and postmenopausal women also concluded that the risk of new fractures, including hip fractures, was significantly reduced in those supplemented compared to controls (82). Interestingly, the three meta-analyses have found that the prevention of fractures by supplemental vitamin D and calcium was limited to institutionalized, older people. Indeed, the risk of fracture was not significantly reduced by vitamin D in community-dwelling seniors (80-82).

Vitamin D supplementation and postural balance, muscle strength, and risk of fall

A meta-analysis of seven observational studies in 840 fallers and 1,330 non-fallers found significantly lower serum 25-hydroxyvitamin D concentrations in fallers than in non-fallers (83). Moreover, another meta-analysis of four cohorts from three observational studies reported a modest yet significant inverse association between vitamin D status and the risk of fall (83). Several randomized controlled trials have examined the impact of vitamin D supplementation on muscle strength, postural balance, or risk of fall in older subjects. A meta-analysis of these trials found limited evidence of an effect of vitamin D supplementation on muscle strength and mobility, based on only one type of test for each outcome. Nevertheless, in a recent randomized, double-blind, placebo-controlled study in 160 postmenopausal women (ages, 50-65 years) with suboptimal vitamin D status (mean serum 25-hydroxyvitamin D concentration <20 ng/mL), supplementation with 1,000 IU/day of vitamin D$_3$ significantly improved vitamin D status, as well as upper and lower limb muscle strength and postural balance parameters (84, 85). The risks of fall and recurrent falls were found to be two- to three-fold greater in women in the control group than in those supplemented with vitamin D$_3$ (85). In contrast, another 12-month randomized controlled study in 200 older adults (of which 58% had a baseline serum 25-hydroxyvitamin D concentration <20 ng/mL) showed no benefits regarding lower extremity function or odds of falling in those supplemented with 2,000 IU/day (+/- 10 µg of calcidiol) compared to those who received 800 IU/day (86). The recently published post-hoc analysis of the ViDA trial found no differences in odds of falling and number of falls reported by 5,108 community-dwelling participants (ages, 50-84 years) regardless of whether they were randomized to receive supplemental vitamin D (100,000 IU/month, i.e. ~3,350 IU/day) or a placebo for a mean 3.4 years (79). Most ViDA participants had serum 25-hydroxyvitamin D concentrations ≥20 ng/mL, which might at least partly explain the lack of an effect of vitamin D on falls (87).

Overall, the current evidence suggests that vitamin D$_3$ supplements of 800-1,000 IU/day may be helpful in reducing falls and fracture rates in older adults. In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should be consumed (see the article on Calcium) (88).

Cancer

Ecologic studies first suggested an association between Northern latitudes, vitamin D deficiency, and cancer incidence (89). Since the 1980s, several prospective cohort studies have examined the association of vitamin D intake or status and various types of cancer. A 2013 systematic review and meta-analysis of 16 prospective studies, including 137,567 subjects, reported an 11% reduction in total cancer incidence and a 17% reduction in cancer mortality with each 20 ng/mL (50 nmol/L) increase in circulating 25-hydroxyvitamin D concentrations. Yet, a sex-based subgroup analysis of eight studies found an inverse association between circulating vitamin D and cancer mortality in women, but not in men (90). In addition, increasing evidence suggests that a few variations in the gene coding for the vitamin D receptor (VDR) might influence individual vitamin D status and subsequently modify the susceptibility to site-specific cancers (91) and influence cancer survival (92). Finally, many malignant tumors have been found to express the VDR, including breast, lung, skin (melanoma), colon, and bone (93), suggesting that they might be susceptible to the effects of vitamin D. Numerous experimental studies have demonstrated that biologically active forms of vitamin D, such as 1α,25-dihydroxyvitamin D and its analogs, upon binding to the VDR, can control cell fate by inhibiting proliferation and/or inducing cell differentiation or death (apoptosis) of a number of cancerous cell types (94).

Colorectal cancer

The geographic distribution of colon cancer mortality resembles the historical geographic distribution of rickets (95), providing circumstantial evidence that decreased sunlight exposure and diminished vitamin D nutritional status may be related to an increased risk of colon cancer. Evidence from observational studies has largely supported this hypothesis. A recent meta-analysis of four prospective cohort studies, four cross-sectional studies, and seven case-control studies found an inverse relationship between circulating vitamin D and incidence of colorectal adenoma — a benign tumor that may transform to become malignant (96). The analysis identified a 32% risk reduction between top versus bottom quantiles of serum 25-hydroxyvitamin D concentrations (96). Additionally, there is strong evidence from meta-analyses of prospective cohort studies to suggest that higher vitamin D intakes and serum 25-hydroxyvitamin D concentrations are associated with reductions in colorectal cancer risk (97-99). The most recent meta-analysis of four prospective cohort, 17 nested case-control, and three case-control studies found a 38% reduced risk of colorectal cancer with high versus low quantiles of circulating 25-hydroxyvitamin D concentrations (100). A dose-response analysis estimated that serum 25-hydroxyvitamin D concentrations of ~20 to 30 ng/mL (compared to ≤12 ng/mL) were associated with a 17% lower risk of colorectal cancer, and the risk was even lower (-35%) with a serum concentration of 55 ng/mL (100). An earlier dose-response analysis based on five nested case-control studies had estimated that serum 25-hydroxyvitamin D concentrations ≥33 ng/mL (compared to ≤12 ng/mL) were associated with a 50% lower risk of colorectal cancer (101).

However, in a seven-year, randomized, double-blind, placebo-controlled trial in 36,282 postmenopausal women participating in the Women's Health Initiative study, a combination of supplemental vitamin D$_3$ (400 IU/day) and calcium (1,000 mg/day) did not lower incidence of colorectal cancer (102). Another randomized controlled trial of vitamin D$_3$ supplementation (1,000 IU/day), with or without calcium supplementation (1,200 mg/day), found no reduction in the risk of colorectal adenoma recurrence over a three-to-five year period, compared to placebo, after initial adenoma removal in participants (103). Whether these daily vitamin D doses are too low to detect any effect on cancer incidence is not clear (101, 104). Additional randomized clinical trials are needed to assess whether vitamin D supplementation could help prevent colorectal cancer. Moreover, it is uncertain whether genetic variations (polymorphisms) in the sequence of genes involved in vitamin D metabolism and function can influence the relationship between vitamin D status and risk of colorectal adenoma or colorectal cancer (105-107).

Finally, growing evidence suggests that adequate vitamin D status may be linked to better survival of colorectal cancer patients. A meta-analysis of five prospective studies found a 35% reduced risk of colorectal cancer-specific mortality in cancer patients with higher serum 25-hydroxyvitamin D concentrations. A dose-response analysis estimated that every 8 ng/mL increase in 25-hydroxyvitamin D concentration was associated with a 10% decrease in colorectal cancer mortality (108).

Breast cancer

Although ecologic evidence suggests that breast cancer mortality rises with increasing latitudes and decreasing sunlight exposure (109), the most current observational data provide little support for an association between vitamin D nutritional status and risk of breast cancer. An early prospective study of women who participated in the First US National Health and Nutrition Examination Survey (NHANES I) found that Caucasian women with adequate sunlight exposure and dietary vitamin D intake had a significantly reduced risk of breast cancer 20 years later (110). Nonetheless, when this study was included in a meta-analysis with nine more recent prospective studies, there was no significant difference in the risk of developing breast cancer between the highest and lowest levels of vitamin D intakes (111). Moreover, whether an association exists between circulating vitamin D concentrations and risk of breast cancer is unclear. One between the highest and lowest levels of vitamin D intakes (111). Moreover, whether an association exists between circulating vitamin D concentrations and risk of breast cancer is unclear. One meta-analysis of 14 observational studies (9,110 cases and 16,244 controls) reported an overall risk reduction of 16% when the highest quantile of serum 25-hydroxyvitamin D concentrations was compared to the lowest. This inverse association was statistically significant in postmenopausal women but not in premenopausal women (112). Yet, another meta-analysis that included a similar set of 14 prospective studies (two studies were different) found no overall association (111). Additionally, a meta-analysis of studies conducted in patients in the early stage of breast cancer identified associations between inadequate vitamin D status and increased risks of recurrence and death (113). Evidence from randomized controlled trials is currently too limited to conclude whether vitamin D supplementation may reduce breast cancer incidence (reviewed in 114).

Nonetheless, three meta-analyses have found an inverse association between circulating vitamin D concentrations and breast cancer-related mortality (111, 115, 116). In one meta-analysis of one retrospective and five prospective cohort studies, the highest versus lowest categories of serum vitamin D concentrations was associated with a 33% reduction in mortality; a dose-response analysis found a 12% reduction per 8 ng/mL increase in serum vitamin D (115).

Finally, current evidence does not suggest that specific genetic variations in the gene coding for the VDR may influence the risk of breast cancer (117, 118).

Other types of cancer

Evidence associating vitamin D status with other types of cancer is currently limited. While incidence of prostate cancer appears to be inversely associated with the availability of sunlight, prospective cohort studies have not generally found significant relationships between serum 25-hydroxyvitamin D concentrations and subsequent risk of developing prostate cancer (119, 120). In fact, some studies have suggested an increased risk of prostate cancer with higher circulating vitamin D concentrations. For example, a nested case-control study of men (622 cases and 1,451 controls) from Scandinavia found a U-shaped relationship between serum 25-hydroxyvitamin D concentrations and prostate cancer risk. In that study, serum 25-hydroxyvitamin D concentrations of 7.6 ng/mL or lower, or 32 ng/mL or higher, were associated with increased prostate cancer risk (121). A meta-analysis of 17 nested case-control studies, three prospective cohort studies, and one retrospective cohort study found a 17% increased risk of prostate cancer in individuals in the highest versus lowest categories of blood 25-hydroxyvitamin D concentrations (122). Potential confounding factors that might explain the detection of a slight increase in prostate cancer cases in men with high circulating vitamin D concentrations have been highlighted in a recent publication (123).

Finally, recent meta-analyses of observational studies found an inverse relationship between vitamin D status and risk of lung cancer (124, 125) and bladder cancer (126, 127). Yet, in the few and often heterogeneous studies published to date, serum 25-hydroxyvitamin D concentrations were not associated with other cancer types, including non-Hodgkin's lymphoma (128), ovarian cancer (129), gastric cancer (130), or skin cancers (131).

Autoimmune diseases

Insulin-dependent diabetes mellitus (type 1 diabetes mellitus), multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) are examples of autoimmune diseases. Autoimmune diseases occur when the body mounts an immune response against its own tissue, rather than a foreign pathogen. In type 1 diabetes mellitus, insulin-producing β-cells of the pancreas are the target of an inappropriate immune response. In MS, the targets are the myelin-producing cells of the central nervous system, and in RA, the targets are the collagen-producing cells of the joints (132). SLE is characterized by the presence of a large spectrum of autoantibodies resulting in potential damage to multiple tissues (133). Autoimmune responses are mediated by immune cells called T cells. The biologically active form of vitamin D, 1α,25-dihydroxyvitamin D, has been found to modulate T cell responses, such that the autoimmune responses are diminished. Ecologic studies have found that the prevalence of autoimmune diseases (particularly for MS; 134) increases as latitude increases, suggesting that lower exposure to UVB radiation and associated decreases in skin vitamin D synthesis may play a role in the pathology of these diseases. Results of several prospective cohort studies also suggest that adequate vitamin D status at different ages (including *in utero*, early childhood, and during adolescence) could possibly decrease the risk of autoimmune diseases.

Type 1 diabetes mellitus

Lower levels of circulating vitamin D have been reported in patients newly diagnosed with type 1 diabetes mellitus compared to age- and sex-matched non-diabetic subjects (135, 136). A greater prevalence of vitamin D insufficiency and deficiency has also been observed in prediabetic children who developed multiple islet autoantibodies (antibodies against insulin-secreting pancreatic cells) compared to autoantibody-negative children. However, a prospective study that followed the cohort of prediabetic children found that their vitamin D status, defined as either insufficient, deficient, or sufficient, was not associated with rate of progression to type 1 diabetes after 5 or 10 years of follow up (137). An earlier prospective cohort study of children born in Finland during the year 1966 and followed for 30 years found that children supplemented with vitamin D during the first year of life had an 88% lower risk of developing type 1 diabetes compared to those receiving no supplementation. Moreover, children suspected of having had rickets (severe vitamin D deficiency) during the first year of life showed a significantly higher risk of developing type 1 diabetes (138). Thus, vitamin D supplementation appears protective against type 1 diabetes onset, and suboptimal vitamin D status in infancy may have long-term effects on immune responses later in life.

There are also limited data suggesting that maternal vitamin D insufficiency during pregnancy may influence the risk of type 1 diabetes in offspring. In a recent case-control study, the risk of childhood onset of type 1 diabetes was more than two-fold greater in children whose mothers had serum 25-hydroxyvitamin D concentrations <21.6 ng/mL (54 nmol/L) during the last trimester of pregnancy compared to children born from women with serum 25-hydroxyvitamin D >35.6 ng/mL (89 nmol/L) (139). Other case-control studies have found that vitamin D supplementation during pregnancy was associated with a lower risk of their children developing diabetes-related autoantibodies (140, 141). However, a larger study conducted in mothers of children at increased genetic risk for diabetes reported no association between the appearance of islet autoantibodies and/or diabetes onset in offspring in the first year of life and maternal vitamin D intake during pregnancy (142). Another case-control study failed to observe a relationship between serum 25-dihydroxyvitamin D during early pregnancy and type 1 diabetes diagnosis in offspring (143). Large prospective studies are needed to establish whether maternal vitamin D status during pregnancy can influence the risk of type 1 diabetes in offspring.

Finally, the relationship of polymorphisms in vitamin D metabolism-related genes and type 1 diabetes is currently under investigation. It has been proposed that specific polymorphisms in genes, such as *CYP27B1* (coding for 25-hydroxyvitamin D_3-1α-hydroxylase) and *VDR*, may be functionally relevant to the action of vitamin D and may thus affect disease susceptibility. In a study conducted in 8,517 children and adolescents with type 1 diabetes and 7,320 control subjects, polymorphisms in genes involved in cholesterol synthesis and vitamin D hydroxylation were linked to circulating vitamin D concentrations and diabetic status (26).

Multiple sclerosis

Low levels of sun exposure and vitamin D deficiency appear to be associated with the development of multiple sclerosis (MS). Poor vitamin D status may compromise the function of specific immune cells critical in the regulation of various immune responses and help trigger autoimmunity in MS (144). Genetic determinants of low vitamin D status have been recently linked to an increased susceptibility to adult-onset MS in a Mendelian randomization analysis of data from the Multiple Sclerosis Genetics Consortium (145). This echoed the results of several observational studies that suggested an association between vitamin D sufficiency and decreased MS risk. A retrospective study of levels of ambient UV radiation and cases of MS conducted in Australia revealed that MS incidence in offspring was inversely correlated to maternal exposure to UV during early pregnancy (146). Sun exposure was also used as a surrogate marker for vitamin D exposure in a recent case-control study that included 1,660 MS patients and 3,050 controls. The authors found that infrequent outdoor activities and the use of sunscreen during early childhood and adolescence were associated with an increased risk of developing MS later in life (147). In a cross-sectional study, sun exposure and intake of cod liver oil (rich in vitamin D) during childhood were linked to later symptom onset among veterans with relapsing MS (148). Additionally, a case-control study in US military personnel, including 257 cases of diagnosed MS, found that Caucasian subjects in the highest quintile of serum 25-hydroxyvitamin D (>39.6 ng/mL) had a 62% lower risk of developing MS compared to the lowest quintile (<25.3 ng/mL) (149). Further, in two large cohorts of over 187,000 US women followed for at least 10 years, vitamin D supplement use (≥400 IU/day) was associated with a 41% reduction in the risk of developing MS (150). Another prospective, uncontrolled study monitored incidence of relapse in relation to vitamin D status in 156 patients with relapsing-remitting MS before and after they were given supplemental vitamin D (100,000 IU/month; 6-42 months, median of 31 months), in addition to first-line immunomodulatory therapy (151). Each 4 ng/mL increase in serum 25-hydroxyvitamin D concentration was associated with a 14.9% decrease in incidence of relapse (151). In a multicenter study conducted in patients newly diagnosed with a clinically isolated syndrome (CIS) and treated with interferon (IFN)-β, vitamin D status was predictive of MS disease activity and progression. Higher serum 25-hydroxyvitamin D concentrations (≥20 ng/mL or ≥50 nmol/L) in the first year following CIS diagnosis predicted a longer time to MS diagnosis, lower number of new lesions, and lower changes in lesion and brain volume during the subsequent four years of follow-up (152). However, a retrospective study suggested that vitamin D status in patients with relapsing-remitting MS had no predictive value regarding the time to conversion to secondary progressive MS, which is characterized by a worsening of disability (153).

Clinical trials have failed to demonstrate any benefit of vitamin D supplementation, alone or in combination with IFN-β treatment, with respect to relapse rates and disability-related symptoms in MS patients (154, 155). In other trials, supplemental vitamin D_3 also failed to demonstrate immunomodulary activities (156-159). In a recent randomized, placebo-controlled trial in 53 IFN-β-treated patients with relapsing-remitting MS, supplementation with vitamin D_3 (7,000 IU/day for four weeks, followed by 14,000 IU/day until week 48) showed little effect on the proportion of some regulatory T and B lymphocytes over the 48-week study period. Vitamin D_3 only appeared to help maintain the proportion of anti-inflammatory CD4⁺ T cells — which decreased in patients given placebo — but failed to enhance their reactivity when stimulated with 1,25-dihydroxyvitamin D *in vitro* (157). In another trial, supplementation with vitamin D_3 (10,400 IU/day for three months) to patients with relapsing-remitting MS was found to reduce the proportion of pro-inflammatory IL-17-producing CD4⁺ T cells, which are thought to play a central role in MS development (160).

Rheumatoid arthritis

Vitamin D deficiency may also be implicated in the etiology and/or progression of rheumatoid arthritis (RA), although evidence is mainly from animal studies. The absence of vitamin D receptors (VDR) in genetically modified mice has been linked to higher levels of inflammation and increased susceptibility to autoimmunity (161). When transgenic mice that spontaneously develop inflammatory arthritis are also deficient in VDR, they develop a more aggressive form of chronic arthritis (162). Also, specific polymorphisms in the *VDR* gene have been linked to an increased susceptibility to RA in certain populations, although how these genetic variants influence vitamin D functionality is not fully understood (163-165). The current data, however, point to a role for vitamin D in modulating the inflammatory process that underlies many chronic diseases, including RA. Several cross-sectional studies in individuals with moderate-to-high levels of inflammation have reported either no association or an inverse association between circulating 25-hydroxyvitamin D concentration and markers of inflammation. Nonetheless, there is a lack of intervention trials to show whether vitamin D supplementation could limit inflammation and reduce disease risk (including RA) in subjects with high inflammation levels (166).

At this time, it remains unclear whether the prevalence of vitamin D deficiency is linked to RA incidence. In a large cohort study of nearly 30,000 postmenopausal US women, subjects with the highest total vitamin D intakes (≥467.7 IU/day) had a 33% lower risk of developing RA after 11 years of follow-up than those with the lowest intakes (<221.4 IU/day) (167). Yet, more recent analyses of two large cohorts of nearly 200,000 US women followed for several decades found no association between reported vitamin D dietary intakes (using food frequency questionnaires) during adolescence or adulthood and incidence of RA later in life (168, 169). Moreover, several studies that explored the relationship between circulating vitamin D and disease activity in RA patients have reported mixed results (reviewed in 170). Yet, two recent meta-analyses of observational studies found an inverse relationship between vitamin D status and disease activity in RA patients, assessed using the Disease Activity Score 28 (DAS28) (171, 172). Finally, there is a dearth of studies exploring the effect of vitamin D supplementation on disease activity in arthritis subjects. A small randomized, double-blind, placebo-controlled study in 22 RA patients failed to demonstrate improvements in disease activity and inflammation level in subjects supplemented with calcium (1,500 mg/day) and high doses of vitamin D_2 (ergocalciferol; averaging over 4,500 IU/day) for a year compared to placebo (173). Another three-month, randomized controlled trial in 41 women with early RA found no additional benefits of supplemental vitamin D_3 (one bolus dose of 300,000 IU) to standard care (methotrexate and glucocorticoids) regarding T-helper lymphocyte enumeration, cytokine production, or clinical parameters including disease activity (174). Supplemental vitamin D also failed to reduce disease recurrence rate in RA patients enrolled in two small randomized controlled trials (175, 176). Since these studies have several limitations, including small sample size, additional research is warranted.

Systemic lupus erythematosus

More prevalent and severe in non-Caucasian populations (Hispanics, African descendants, and Asians) (177), systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous clinical manifestations. The disease can potentially affect most tissues and organs, including skin (skin rash and photosensitivity), kidneys (nephritis), and joints (arthritis). There is evidence of a role for vitamin D in the prevention of SLE in animal models (178). Interestingly, a recent meta-analysis of 11 case-control studies found that specific *VDR* polymorphisms were linked to SLE in Asians particularly (179). However, the functional relevance of such genetic variants is not known (180). Analyses of two large prospective cohort studies of nearly 200,000 US women failed to show an association between dietary vitamin D intake (measured by food frequency questionnaire) during adolescence or adulthood and incidence of SLE later in life (168, 169).

Yet, a suboptimal vitamin D status is commonly observed in subjects with SLE, and this is partly explained by the lack of sunlight exposure, which tends to aggravate disease symptoms (181, 182). Serum concentrations of 25-hydroxyvitamin D were inversely correlated with measures of disease activity in a cohort of 378 patients with SLE (183). The correction of vitamin D insufficiency with high levels of vitamin D_3 (100,000 IU/week for one month followed by 100,000 IU/month for six months) in 20 subjects with SLE was linked to a reduction in signs of immune imbalance and in levels of autoantibodies typically detected in SLE, suggesting a therapeutic value for vitamin D in disease treatment (184). Another prospective study conducted in 52 vitamin D-deficient patients with cutaneous lupus erythematosus (a type of lupus with skin disorders only) reported a reduction in disease severity in the group supplemented with vitamin D_3 (1,400 IU/day initially, followed by 800 IU/day) and calcium for one year compared to untreated patients (185). Supplementation with vitamin D_3 (200 IU/day for one year) was also able to reduce the level of inflammatory cytokines in a randomized, placebo-controlled study conducted in 267 patients with SLE (186). In another randomized, placebo-controlled trial, supplementation with vitamin D_3 (50,000 IU/week for six months) improved SLE disease activity index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) scores, as well as some measures of fatigue in young adults with juvenile-onset SLE (187). However, in two other recent studies, supplementation with vitamin D_3 (weekly/monthly bolus doses equivalent to ~800 to 7,000 IU/day for 6 to 24 months) improved vitamin D status in SLE patients but failed to show any benefit regarding disease activity (188, 189). While oral vitamin D administration to SLE patients is well tolerated, its efficacy remains questionable and deserves further investigation in clinical trials.

Summary

Thus, evidence from human epidemiological studies suggests that while it cannot yet be concluded that vitamin D supplementation is beneficial in prevention or treatment of autoimmune disease, it is reasonable to assume that correcting vitamin D insufficiency and maintaining sufficient levels could possibly help decrease disease risk (190).

Cardiovascular disease

Hypertension (high blood pressure)

Hypertension is a well-known risk factor for cardiovascular disease (CVD) (191). The results of observational and clinical studies suggest a role for vitamin D in lowering blood pressure, which may be partly explained by the fact that 1α,25-dihydroxyvitamin D inhibits renin synthesis (see Function). Thus, vitamin D deficiency and subsequent upregulation of the renin-angiotensin system may contribute to high blood pressure and CVD risk. It has also been suggested that elevated PTH concentrations may increase the risk of hypertension and CVD (6). Yet, in a recent prospective cohort study of 3,002 individuals (mean age, 59 years at baseline), the incidence of hypertension, which affected 41% of participants during the nine year follow-up period, was not higher in those with serum 25-hydroxyvitamin D concentrations lower than 20 ng/mL and was only marginally associated with elevated PTH concentrations (192). Nevertheless, a meta-analysis of seven prospective studies, including a total of 48,633 participants with nearly 5,000 incident hypertension cases, found a 30% lower risk of hypertension in those in the top versus bottom tertiles of serum 25-hydroxyvitamin D concentrations. The dose-response analysis estimated that every 10 ng/mL increase in serum 25-hydroxyvitamin D concentration was associated with a 12% lower risk of hypertension (193). Another meta-analysis of four prospective and 14 cross-sectional studies also reported an inverse relationship between circulating 25-hydroxyvitamin D and hypertension (194).

Endothelial dysfunction

Vascular endothelium dysfunction, which contributes to an increased risk of cardiovascular disease (CVD), is common in patients with chronic kidney disease (CKD) (195). In CKD patients, abnormal endothelial function is associated with low values of flow-mediated dilation (FMD) of the brachial artery, a surrogate marker of vascular health. In a recent study conducted in subjects with mild-to-moderate CKD, serum 25-hydroxyvitamin D concentrations were positively associated with FMD values, suggesting a link between suboptimal vitamin D status and endothelial dysfunction (196). In a preliminary intervention study, 26 patients with moderate CKD and vitamin D insufficiency (mean value, 17.2 ng/mL) were supplemented twice with 300,000 IU of vitamin D_3 (at weeks 1 and 8) and followed for a total of 16 weeks. Vitamin D supplementation nearly doubled serum 25-hydroxyvitamin D concentrations and decreased PTH concentrations by 68.5%; improved vitamin D status was accompanied by increased FMD values and reduced levels of endothelial dysfunction markers (197). A recent meta-analysis of 12 small randomized controlled trials in participants at high risk for CVD found a significant increase in FMD with vitamin D supplementation (daily doses, 2,500-5,000 IU; weekly dose, 50,000 IU; monthly dose, 60,000 IU; single-bolus doses, 100,000-200,000 IU) for eight weeks to six months (198).

Cardiovascular events in observational studies and clinical trials

To date, the many epidemiological studies investigating the relationship between vitamin D and outcomes of CVD have provided mixed results (reviewed in 199). Recent Mendelian randomization studies found no association between genetically low serum 25-hydroxyvitamin D concentrations and risks of coronary heart disease, ischemic heart disease, or myocardial infarction (200, 201), suggesting that associations reported in observational studies may be due to confounding or reverse causation. In the RECORD trial in 5,292 older people (see Osteoporosis), supplementation with 800 IU/day of vitamin D_3 (± calcium) reduced the risk of first cardiac failure but had no effect on the risk of myocardial infarction and stroke compared to supplementation with calcium alone or placebo (202). Data on the effect of vitamin D supplementation on cardiovascular events were collected from 21 randomized controlled studies (including the RECORD trial) in 13,033 participants (≥60 years old) and combined in a meta-analysis (202). No effect of vitamin D (including vitamin D analogs) was found for major cardiovascular events, including heart failure, myocardial infarction, and stroke over follow-up periods of 1 to 6.2 years (202). However, caution is advised when interpreting these results since the trials were initially designed to evaluate the effect of vitamin D on bone health, and cardiovascular outcomes were not primary endpoints. Several randomized controlled trials exploring the effect of vitamin D supplementation on CVD risk are currently underway (203), including two large trials, the Vitamin D and Omega-3 Trial (VITAL) in the US (204) and the D-Health trial in Australia (205). The results of one randomized controlled trial, the Vitamin D Assessment (ViDA) trial in New Zealand, were recently published. The total number of CVD events and time to first CVD event during follow-up did not differ between those supplemented with vitamin D_3 (initial dose of 200,000 IU for the first month followed by monthly doses of 100,000 IU) and those given a placebo for a median 3.3 years (206).

Type 2 diabetes mellitus

People with metabolic syndrome are at increased risk for type 2 diabetes mellitus (noninsulin-dependent diabetes mellitus) and cardiovascular disease (CVD). Metabolic syndrome refers to several metabolic disorders, including dyslipidemia, hypertension, insulin resistance, and obesity. A recent study found that the prevalence of type 2 diabetes was associated with low levels of serum 25-hydroxyvitamin D (<30 ng/mL) in 1,801 patients with metabolic syndrome. During an eight-year follow-up period, lower risks of all-cause mortality (72% lower risk) and CVD-specific mortality (64% lower risk) were reported in individuals with serum 25-hydroxyvitamin D concentrations over 30 ng/mL (75 nmol/L) when compared to those with concentrations below 10 ng/mL (25 nmol/L) (207).

In healthy people, vitamin D sufficiency is positively correlated with insulin sensitivity and adequate pancreatic β-cell function. Conversely, vitamin D deficiency might affect glucose homeostasis and cause impaired glucose tolerance and insulin resistance (208). In a cross-sectional study conducted in 12,719 adults, of whom 4,057 had prediabetes (i.e., an increased risk of developing type 2 diabetes), the prevalence of prediabetes was associated with lower concentrations of serum 25-hydroxyvitamin D (≤32.4 ng/mL). Subjects with the lowest concentrations of serum 25-hydroxyvitamin D (≤17.7 ng/mL) were more likely to be current smokers, obese, and have hypertension (209). Vitamin D insufficiency in high-risk individuals may accelerate the progression to overt diabetes. In a prospective study of 2,378 middle-aged men and women followed for 8 to 10 years, the risk for progression to type 2 diabetes from prediabetes was 62% lower in women and 60% lower in men in the highest compared to the lowest quartile of circulating vitamin D (>28.4 ng/mL vs. <18.5 ng/mL). A dose-response analysis measured an average 23% reduction in the risk of progression to type 2 diabetes for every 4 ng/mL (10 nmol/L) increment in serum 25-hydroxyvitamin D concentration (210). A recent review and meta-analysis of 18 prospective cohort studies, including over 210,000 participants followed for a median period of 10 years, found that individuals in the top third of vitamin D levels (reported as either circulating vitamin D or dietary intakes) had lower risks of developing type 2 diabetes (19% lower risk) and metabolic syndrome (14% lower risk) compared to those in the bottom third (211). In another meta-analysis of nine prospective studies, including 28,258 older people (mean age, 67.7 years), lower versus higher circulating vitamin D concentrations at baseline were found to be associated with a 17% higher risk of developing type 2 diabetes over a median follow-up period of 7.3 years (212). Currently, limited evidence suggests that vitamin D supplementation may improve insulin sensitivity in individuals with glucose intolerance or manifest type 2 diabetes (213-216). There is a need for well-designed clinical trials to examine whether maintaining adequate vitamin D levels can prevent adverse metabolic outcomes in healthy and at-risk individuals.

Neurodegenerative diseases

Cognitive impairment and Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, characterized by the presence of extra-neuronal β-amyloid plaques and intra-neuronal Tau protein aggregates (known as neurofibrillary tangles) in the brain. Mechanistic models currently investigated in animal research suggest that vitamin D deficiency or disorders of vitamin D metabolism and/or the disruption of the vitamin D-VDR pathway in the cerebral regions of the cortex and hippocampus may be involved in the degeneration of neurons and loss of cognitive functions (217). Experimental evidence supporting a role for vitamin D in calcium channel regulation, neuroprotection, and immunomodulation in the central nervous system also implies that low vitamin D status may precede or contribute to cognitive dysfunction with age (218).

A number of observational studies have examined cognitive decline and degenerative brain disease in the elderly in relation to dietary intake of vitamin D and serum 25-hydroxyvitamin D concentration. In a large French cohort study on osteoporosis and hip fractures in postmenopausal women, impairments in global cognitive performance, assessed with the Pfeiffer Short Portable Mental State Questionnaire (SPMSQ), were associated with lower dietary intakes of vitamin D (<1,400 IU/week vs. ≥1,400 IU/week) in 5,596 elderly women (mean age, 80.5 years) (219). A seven-year follow-up study of a subgroup of 498 women indicated that the risk of Alzheimer's disease (but not other types of dementia) was 77% lower in those in the highest versus the lowest quintiles of vitamin D dietary intakes at baseline (220). Some, but not all, observational studies have found an association between low serum 25-hydroxyvitamin D concentrations and mild cognitive impairment in older adults (219, 221, 222). The cross-sectional and longitudinal analysis of two prospective studies, which included 1,604 men (223) and 6,257 women (224) aged 65 and over, reported a 60% greater odds of cognitive impairment at baseline and a 58% increased risk of cognitive decline during a four-year follow-up period in women, but not in men, with vitamin D deficiency (circulating 25-hydroxyvitamin D <10 ng/mL vs. ≥30 ng/mL). In the nested case-control, multiethnic, Singapore Kidney Eye Study, which included 2,273 individuals (mean age, 70.4 years), serum 25-hydroxyvitamin D concentrations were inversely correlated with cognitive deficits affecting retrograde episodic memory, semantic memory, and orientation in time, as assessed by the Abbreviated Mental Test (AMT) (225).

Yet, systematic reviews and meta-analyses of observational studies have given mixed results regarding the association of vitamin D status with cognitive performance and AD (226-230). Moreover, the recent analysis of data from 1,182 men followed for 18 years in the Uppsala Longitudinal Study of Adult Men (ULSAM) failed to find associations of genetic determinants of vitamin D synthesis, vitamin D intakes, and plasma 25-hydroxyvitamin D concentrations with risks of cognitive impairments, AD, vascular dementia, or all-cause dementia (231). In contrast, another Mendelian randomization study associated genetic determinants of low vitamin D status to higher risk of AD in the International Genomics of Alzheimer's Project dataset (17,008 AD cases and 37,154 healthy cases) (232).

Nevertheless, the prevalence of vitamin D insufficiency/deficiency ranges between 70% and 90% in older adults, and correcting low concentrations of serum 25-hydroxyvitamin D may help improve cognitive processes, in particular executive functions (233). In a small, non-randomized controlled study in an outpatient clinic, global cognitive function was assessed at baseline and after 16 months in 20 patients supplemented with 800 IU/day (or 100,000 IU/month) of vitamin D and in 24 control subjects. The supplementation of outpatients with vitamin D resulted in the correction of low vitamin D status (average serum 25-hydroxyvitamin D concentration was 16.8 ng/mL at baseline and 30 ng/mL at 16 months) and was associated with a significantly improved scoring in cognition tests compared to the non-supplemented group (234). In a small randomized, placebo-controlled clinical trial in 32 mild-to-moderate AD patients receiving nasal insulin, high doses of vitamin D_2 supplementation for eight weeks (up to 36,000 IU/day) did not significantly improve cognitive performance compared to low doses (1,000 IU/day) (235). More research is needed to investigate a causal relationship between vitamin D repletion and potential long-term cognitive benefits in older adults. Further, it is of great importance to evaluate whether correcting vitamin D deficiency in cognitively impaired subjects can improve the impact of anti-dementia therapy (236).

Parkinson's disease

Parkinson's disease (PD) has been associated with a high prevalence of vitamin D insufficiency among patients, especially those with greater mobility problems (237). A case-control study of 296 outpatients with a mean age of 65 years indicated that 23% of PD subjects had serum 25-hydroxyvitamin D concentrations lower than 20 ng/mL compared to 16% and 10% of AD and healthy individuals, respectively (238). In a prospective cohort study conducted among 3,173 men and women aged 50-79 years and free of PD at baseline, individuals in the highest quartile of serum 25-hydroxyvitamin D (≥20 ng/mL for women and ≥22.8 ng/mL for men) had a 67% lower risk of PD compared to those in the lowest quartile (≤10 ng/mL for women and ≤11.2 ng/mL for men) (239). Meta-analyses pooling data from observational studies all showed that vitamin D inadequacy was more likely reported in subjects with PD than in healthy controls (240-242).

In a randomized, double-blind, placebo-controlled study, 112 PD patients (mean age, 72 years) on standard PD treatment were supplemented with 1,200 IU/day of vitamin D or a placebo for 12 months. Vitamin D supplementation nearly doubled serum 25-hydroxyvitamin D concentration (from mean of 22.5 ng/mL to 41.7 ng/mL) in supplemented subjects and limited the progression of PD, as indicated by a greater proportion of patients who showed no worsening (as assessed by the Hoehn and Yahr stage and the United Parkinson Disease Rating Scale part II) in the supplemented group compared to the placebo group (243). It is not known whether vitamin D insufficiency has a role in the pathogenesis of the disease, but the repletion of vitamin D may provide health benefits that go beyond the prevention and/or the treatment of PD. For example, vitamin D deficiency may contribute to the increased risk of osteoporosis and bone fracture in individuals with neurologic disorders, including PD and multiple sclerosis (244-246). Interestingly, sunlight exposure was found to be associated with improved vitamin D status, higher bone mineral density of the second metacarpal bone, and lower incidence of hip fracture in a prospective study conducted in 324 elderly people with PD (247).

Adverse pregnancy outcomes

A systematic review and meta-analysis of 31 observational studies on maternal vitamin D status and pregnancy outcomes indicated that vitamin D insufficiency may be associated with gestational diabetes mellitus, preeclampsia, and bacterial vaginosis in pregnant women. Low maternal serum vitamin D during pregnancy was also linked to an increased risk for small-for-gestational age infants and low-birth-weight infants, but not for Cesarean section (248). However, the number of intervention trials is currently too limited to draw conclusions as to whether vitamin D supplementation during pregnancy might reduce the incidence of the above-mentioned adverse outcomes (249).

Gestational diabetes mellitus

Abnormal hyperglycemia due to pancreatic β-cell dysfunction characterizes the onset of gestational diabetes mellitus (GDM) in pregnant women without known type 2 diabetes mellitus. This condition is associated with serious adverse maternal outcomes, including preeclampsia, high risk of Cesarean delivery, and life-long increased risk of developing metabolic syndrome and type 2 diabetes mellitus. GDM may also contribute to increased risks of fetal macrosomia (excessive birth weight), neonatal hypoglycemia, infant respiratory distress, and increased life-long risk for obesity, glucose intolerance, type 2 diabetes mellitus, and cardiovascular disease in the offspring (reviewed in 250).

A recent prospective study conducted in 655 pregnant women found that the mean serum 25-hydroxyvitamin D concentration during the first trimester of pregnancy was significantly lower in 54 women who developed incident GDM compared to the rest of the cohort (23 ng/mL vs. 25.4 ng/mL). After multiple adjustments for confounding factors of vitamin D status and GDM risk (including overweight/obesity and prior history of type 2 diabetes and GDM), the study found each 7.5 ng/mL decrease in serum 25-hydroxyvitamin D concentration during early pregnancy was associated with a 48% higher risk of developing GDM (251). Low serum 25-hydroxyvitamin D concentrations (<29.4 ng/mL) during the second trimester of pregnancy were also associated with GDM incidence in a nested case-control study of 118 women with GDM and 219 matched control subjects (252). Five meta-analyses (248, 253-256), including observational studies of moderate-to-high quality, also reported that maternal serum vitamin D concentrations during pregnancy were inversely related to the risk of developing GDM despite evidence of bias amongst studies, such as the use of different methods for serum 25-hydroxyvitamin D measurement, measures done in different trimesters, and different criteria to assess GDM (reviewed in 257).

Further, evidence for the role of vitamin D in glucose regulation during pregnancy was reported in a small randomized, double-blind, placebo-controlled trial in 54 pregnant women diagnosed with GDM. The supplementation with 50,000 IU of vitamin D_3 twice during a six-week period (at day 1 and day 21) resulted in significantly lower fasting plasma glucose and serum insulin concentration, reduced insulin resistance, and improved insulin sensitivity compared to placebo (258). This suggests that vitamin D deficiency may adversely affect glucose tolerance during pregnancy and contribute to the onset of GDM. Yet, the potential benefits of vitamin D supplementation in the prevention of glucose intolerance and GDM during pregnancy have not been assessed. A multicentered, randomized controlled trial (DALI) is ongoing in Europe to evaluate the effects of vitamin D and lifestyle interventions (healthy eating and physical activity) on the metabolic status of pregnant women at risk of GDM (inclusion criteria: pre-pregnancy BMI ≥29 kg/m^2) (259). Preliminary findings suggest that healthy eating and physical activity can help lower gestational weight gain, when compared to standard-of-care; however, these lifestyle changes are unlikely to reduce the risk of GDM among obese pregnant women (260). The results regarding the effect of vitamin D supplementation in the DALI study are yet to be published.

Health outcomes in offspring

During pregnancy, increased intestinal calcium absorption and mobilization of calcium from the skeleton allows accretion of calcium within the fetal skeleton. Yet, observational studies that examined the relationship between maternal vitamin D status and measures of fetal bone growth have not provided consistent results (261, 262). In addition, recent data from the Maternal Vitamin D Osteoporosis Study (MAVIDOS) suggested no difference in whole-body bone mineral content (BMC) of newborns from mothers randomized to daily supplementation with either vitamin D_3 (1,000 IU) or placebo from <17 weeks' gestation until delivery (263). Further, the risk of fracture in Danish children ages 10 to 18 years was similar regardless of whether their mothers were exposed to extra vitamin D from fortification during pregnancy (264). While maternal vitamin D supplementation during pregnancy effectively prevents the neonate's risk of vitamin D deficiency at birth (265), there is little evidence that neonatal vitamin D status influences the risk of fracture later during childhood (266).

A few observational studies have given rather weak evidence in support of a relationship between maternal vitamin D sufficiency during pregnancy and incidence of respiratory conditions and allergies in children (267). A randomized controlled trial found that the supplementation of 108 pregnant women in the third trimester (at week 27 of gestation until delivery) with either 800 IU/day or a bolus dose of 200,000 IU of vitamin D_3 did not decrease the risk of wheezing, allergic rhinitis, food allergy diagnosis, lower respiratory tract infections, or eczema in offspring at three years of age compared to placebo (N=50) (268). A more recent double-blind, randomized controlled trial found that vitamin D_3 supplementation of 295 Danish pregnant women, from weeks 22 to 26 of gestation until delivery, with 2,800 IU/day (70 μg/day) — compared to 400 IU/day (10 μg/day) of vitamin D_3 (i.e., the current recommendation in Denmark) (N=286) — reduced the risk of troublesome episodes of lung symptoms by 17% in offspring during the first three years of life (269). However, no differences were reported regarding the risk of persistent wheeze, asthma, allergic sensitization, respiratory tract infections, or eczema between treatment and control groups (269). In a similar randomized, double-blind, controlled trial — the Vitamin D Antenatal Asthma Reduction Trial — conducted in 777 US pregnant women with a history of asthma, allergic rhinitis, or eczema (or whose partner had such an history), supplementation with 2,400 IU/day (60 μg/day) or 400 IU/day (10 μg/day) did not result in differences in the risk of developing asthma or recurrent wheezing in their children at age three years (270). Despite the lack of significance reported in individual studies, the pooled analysis of the three trials found a 19% reduction in the risk of recurrent wheeze in children whose mothers received high-dose versus low-dose vitamin D supplementation during pregnancy (271). In a cohort of 378 mother-child pairs, high serum 25-hydroxyvitamin D concentrations measured in the 34th week of pregnancy were associated with an increase in food allergy of the child during the first two years of life, warranting careful evaluation of the safety of vitamin D supplementation during pregnancy (272).

Since vitamin D insufficiency has been linked to autoimmunity (see Autoimmune diseases), it has also been proposed that poor maternal vitamin D status during pregnancy may contribute to an increased risk of autoimmune diabetes (insulin-dependent type 1 diabetes mellitus) in the offspring. Yet, the results of a study of 3,723 children at high genetic risk for type 1 diabetes and followed for a mean 4.3 year-period found that maternal intake of vitamin D (from food and/or supplements) during the third trimester of pregnancy (assessed through food frequency questionnaires) was not associated with advanced β-cell autoimmunity or clinical diabetes (142). In a nested case-control study, there was no difference in mean serum concentration of 25-hydroxyvitamin D during the first trimester of pregnancy between 343 mothers of children with type 1 diabetes and 343 control mothers (143). A follow-up study suggested that specific maternal *VDR* polymorphisms, rather than vitamin D status, may be linked to an increased susceptibility to developing type 1 diabetes in children (273). Another nested case-control study (119 mothers of children with type 1 diabetes and 129 control mothers) found an inverse association between maternal vitamin D-binding protein — but not 25-hydroxyvitamin D — concentration during the third trimester of pregnancy and the risk of type 1 diabetes in children (274). At present, there is no established causality between maternal vitamin D status during pregnancy and risk of autoimmune disease in offspring.

Acute respiratory infections

More than 200 viruses are responsible for causing familiar infections of the upper respiratory tract (URT), known as the common cold, resulting in symptoms of nasal congestion and discharge, cough, sore throat, and sneezing (275). The analysis of cross-sectional data from 18,883 participants (ages 12 years and older) of the Third US National Health and Nutrition Examination Survey (NHANES III) reported an inverse relationship between serum 25-hydroxyvitamin D concentrations and recent (self-reported) URT infection (URTI). Compared to levels of circulating vitamin D of 30 ng/mL or above, the risk of URTI was 24% higher in individuals with concentrations between 10 and 29 ng/mL and 36% higher in those with levels below 10 ng/mL (276). A subgroup analysis indicated that low concentrations of serum 25-hydroxyvitamin D in subjects with asthma and chronic obstructive pulmonary disease (COPD) were linked to a greater susceptibility to URTI when compared to people without pulmonary disease.

In a randomized, double-blind, placebo-controlled trial conducted in 322 healthy adults (ages ≥18 years), supplementation with monthly doses of vitamin D_3 (200,000 IU for the first two months and 100,000 IU for the following 16 months) significantly raised the mean serum 25-hydroxyvitamin D concentration (from 29 ng/mL to 48 ng/mL) in the intervention group but did not decrease the occurrence of URTI compared to placebo (277). Moreover, in a larger, multicenter, four-arm clinical trial in 2,259 subjects (aged 45-75 years) with a history of colorectal adenoma, daily vitamin D_3 supplementation of 1,000 IU did not reduce the number or the duration of URTI episodes during winter or the rest of the year, even among participants with the lowest serum 25-hydroxyvitamin D concentrations at baseline (278). In addition, the post-hoc analysis of data from a randomized, placebo-controlled trial in 644 individuals (ages 60-84 years) found that monthly supplementation with 30,000 IU or 60,000 IU of vitamin D_3 for a maximum period of one year did not significantly decrease the rate of antibiotic prescriptions for bacterial airway infections. The stratified analysis, however, found that doses of 60,000 IU/month reduced the risk of using antibiotics in participants ≥70 years old by 47% (279). In addition, compared to placebo, the supplementation of pregnant women with vitamin D_3 (with 2,000 IU/day) for three months until birth followed by the supplementation of their infants (800 IU/day) from birth to six months of age significantly reduced the number of acute respiratory infections after the intervention period in children 6 to 18 months old (280). Interestingly, despite significant heterogeneity among trials, the pooled analysis of these data with that of 21 additional trials suggested an overall 12% reduction in incidence of URTI with vitamin D_3 given as bolus doses (every week, month, or every three months), daily doses, or a combination of bolus and daily doses (281). Subgroup analyses revealed a 42% reduction in URTI risk with vitamin D_3 supplementation in subjects with baseline serum 25-hydroxyvitamin D concentrations <10 ng/mL, while there was no protective effect of vitamin D_3 in those with concentrations ≥10 ng/mL. Moreover, large bolus doses (≥30,000 IU) were found to be ineffective compared to daily or weekly doses such that, in subgroup analyses that excluded bolus doses, daily and weekly vitamin D_3 regimens appeared to be protective against URTI regardless of baseline vitamin D status. Finally, the effect of vitamin D_3 supplementation on URTI did not appear to vary with age, BMI, the presence of asthma or COPD, and flu vaccination status (281).

The findings of a large clinical trial in New Zealand, the Vitamin D Assessment (ViDA) Study, confirmed the ineffectiveness of large bolus doses of vitamin D in reducing the risk of acute respiratory infections (282). In this double-blind, placebo-controlled trial in 5,110 older adults (ages 50-84 at baseline), supplementation with an initial dose of 200,000 IU of vitamin D_3 followed by 100,000 IU/month of vitamin D_3 for a median of 3.3 years had no effect on the incidence of (self-reported) acute respiratory infections (HR, 1.01; 95% CI, 0.94-1.07). Upon data stratification by vitamin D status, a similar null result (HR, 1.08; 95% CI, 0.95-1.23) was seen in study participants with blood vitamin D concentrations ≤20 ng/mL (≤50 nmol/L; 282).

The recently completed VITAL (Vitamin D and Omega-3 Trial) may provide additional evidence of an effect of daily dosing (2,000 IU/day of vitamin D) on risk of airway infections in older adults, although the prevention of infectious disease is a secondary outcome in the trial (204, 283, 284).

In a trial in preschool-age children, vitamin D supplementation with 2,000 IU/day for at least four months did not decrease the incidence (285) or severity (286) of URTI in winter compared to supplementation with 400 IU/day for at least four months. Supplementation with 2,000 IU/day led to significantly higher mean serum 25-hydroxyvitamin D concentrations compared to the lower dose (48.7 ng/mL vs. 36.8 ng/mL), but the 400 IU dose may have been sufficient to prevent URTI in these young children (285). In a placebo-controlled trial in 1,300 healthy children and adolescents in rural Vietnam (baseline 25-hydroxyvitamin D concentrations of 26 ng/mL for both the control and intervention group), supplementation with 14,000 IU/week of vitamin D for eight months significantly reduced the incidence of non-influenza viral respiratory infections by 24%, but not the incidence of influenza A or B infection (287).

Coronavirus disease, COVID-19

The coronavirus disease, COVID-19, is caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus originated in Wuhan, China in late 2019 and rapidly spread throughout the world causing a global pandemic. Flu-like symptoms, including cough, fever, fatigue, and difficulty breathing, as well as several other diverse symptoms characterize COVID-19 (see the websites of the CDC and the WHO). The effects of the disease vary widely, with the most severe resulting in pneumonia, respiratory distress, and death. Some individuals infected with SARS-CoV-2, however, are asymptomatic but can transmit virus to others (288). Moreover, SARS-CoV-2 infected individuals can spread disease before they experience symptoms (i.e., presymptomatic transmission) (289), placing importance on public health measures like hand washing, face mask wearing, social distancing, and testing and contact tracing to curtail the pandemic.

A number of observational studies have examined the correlation of vitamin D status and COVID-19 incidence, with most — but not all (290-292) — finding vitamin D deficiency or insufficiency associated with an increased risk of SARS-CoV-2 infection. In a retrospective cohort study of more than 191,000 US residents administered a SARS-CoV-2 test during a three-month period in spring 2020, SARS-CoV-2 positivity was strongly associated with a lower serum 25-hydroxyvitamin D concentration, measured at a single point in the 12 months prior to the viral test (293). In this study, each 1 ng/mL increment of serum 25-hydroxyvitamin D was linked to a 1.6% lower risk of SARS-CoV-2 positivity, with the risk being the lowest at serum concentrations of 55 ng/mL and above (293). In a retrospective, population-based study among 7,807 people in Israel, including 782 SARS-CoV-2 positive cases, plasma 25-hydroxyvitamin D concentrations below 30 ng/mL were associated with a 50% higher risk of SARS-CoV-2 infection compared to higher vitamin D concentrations (294). The vitamin D status assessment in this study was done prior to the viral testing, but details on the time frame are lacking. The temporal relationship of the vitamin D status measure and COVID diagnostic test is also a concern in an analysis of a large dataset from the UK Biobank, which found vitamin D status was not associated with SARS-CoV-2 infection: the study utilized vitamin D status assessments done 10 to 14 years prior to the COVID-19 diagnostic test (291). Consistent with findings of most available studies, a small retrospective cohort study (295) and five case-control studies (296-300) reported an inverse association of vitamin D status and SARS-CoV-2 infection. A 2021 meta-analysis of 10 observational studies, including 361,934 participants, reported an association between vitamin D insufficiency or deficiency and increased risk of COVID-19 (OR, 1.43; 95% CI: 1.00-2.05), although heterogeneity across studies was high (301). Further, in an analysis of data from the UK Biobank, regular use of vitamin D supplements was found to be associated with a 34% lower risk of SARS-CoV-2 infection compared nonusers of vitamin D supplements (292).

Additionally, most of the available observational research suggests an association between low vitamin D status and COVID-19 severity, with studies finding vitamin D deficiency linked to an increased risk of disease severity, as measured by need for hospitalization, intensive care unit admission (302), stage of pneumonia (in men but not in women; 303), need for non-invasive ventilation (304), need for invasive mechanical ventilation (305), or a combination of these and other indicators (297). Another study found that insufficient vitamin D status, defined as plasma 25-hydroxyvitamin D concentrations below 30 ng/mL, was associated with an increased likelihood of COVID-related hospitalization, but the association failed to reach statistical significance ($p=0.061$) except in a subanalysis of individuals over 50 years of age (OR, 2.71; 95% CI: 1.55-4.78; $p<0.001$) (294). In contrast to most of the evidence to date, one case-control study found vitamin D deficiency was not linked to COVID-19 severity (298). Further, a few studies have looked at the relationship of vitamin D status and COVID-19 mortality, with three finding vitamin D deficiency to be associated with an increased risk of death (303, 305, 306) and two finding no association (304, 307), although one of the studies finding no association used vitamin D status measurements more than 10 years prior to the COVID-19 diagnostic testing (307).

Since there are several known risk factors for severe illness from COVID-19, including advanced age, obesity, and preexisting type 2 diabetes or cardiovascular disease (308), it is important for observational studies to control for potential confounders. Two quasi-experimental studies reported that bolus supplementation with vitamin D_3 (either 50,000 IU per month or 80,000-100,000 IU every two to three months) prior to or during SARS-CoV-2 infection was associated with a less severe illness and improved survival in frail elderly COVID-19 patients (309, 310). A number of randomized controlled trials of vitamin D supplementation in COVID-19 prevention and treatment are currently underway; the results of these trials will inform on the causality of the association. Nevertheless, the currently available data indicate that improving vitamin D status through supplementation represents a modifiable risk factor for COVID-19.

Disease Treatment

Atopic dermatitis

Atopic dermatitis or eczema is particularly prevalent in industrialized countries, affecting 10%-20% of children and 1%-3% of adults. Atopic dermatitis is a chronic inflammatory skin disorder characterized by dry and pruritus (itchy) areas of the skin in affected subjects. Local skin inflammation and immune dysfunction can damage the epidermal barrier and increase the susceptibility to skin infections and atopic reactions in affected individuals. The disease is often associated with other atopic diseases, including food allergies, asthma, and allergic rhinitis (311).

While the etiology of the disease is not fully elucidated, it has been suggested that vitamin D deficiency might contribute to the onset and/or the severity of the disease (312). Recently, using large-scale datasets from Caucasian people of European descent, including the UK Biobank resource (313) and the SUNLIGHT (35), the GABRIEL asthma (314), and EAGLE eczema (315) consortia, a Mendelian randomization study found no association between genetically low serum 25-hydroxyvitamin D concentrations and risks of atopic dermatitis, asthma, or high serum immunoglobulin (Ig)-E concentrations (316).

A number of randomized controlled studies have examined whether vitamin D might be an effective adjunct tool in disease management, possibly through regulating local inflammatory reactions and stimulating antimicrobial activities in the skin. Moreover, the beneficial effect of phototherapy observed in specific cases of atopic dermatitis may be partly mediated by the action of vitamin D (311). In a small randomized, double-blind, placebo-controlled study in 45 patients with atopic dermatitis and low vitamin D status (70% of subjects had serum 25-hydroxyvitamin D concentrations <20 ng/mL), daily administration of 1,600 IU of oral vitamin D_3, alone or together with 600 IU/day of vitamin E, for a period of 60 days significantly reduced the extent and intensity of eczema, as assessed by the SCORAD (SCORing Atopic Dermatitis) score (317). Vitamin D_3 (1,600 IU/day for 60 days) also improved vitamin D status and reduced disease severity in 53 patients with atopic dermatitis in another small randomized trial (318). More recently, vitamin D_3 (1,000 IU/day for one month) improved the severity of winter-related atopic dermatitis in Mongolian children, as shown by changes in Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) scores (319). A meta-analysis of four small trials (including those cited above) confirmed that supplemental vitamin D can lead to measurable clinical improvements in affected individuals (320). Larger trials are needed to strengthen these preliminary findings and determine the most appropriate and effective supplementation regimen. Of note, topical treatment of psoriasis with vitamin D analogs has been approved by the US Food and Drug Administration (FDA) and may be effective in the management of other skin disorders (321).

Inflammatory bowel diseases

Several ill-defined environmental and genetic factors are thought to contribute to the development of the inappropriate immune response to the intestinal microbiota that causes ulcerative colitis (UC) and Crohn's disease (CD). While specific *VDR* polymorphisms may be linked to an increased susceptibility to developing UC and CD (322), higher vitamin D intakes and predicted circulating levels were found to be associated with a reduced incidence of UC and CD in a large cohort of 72,719 women (323). A meta-analysis of six observational studies found an inverse association between vitamin D status and severity of CD (324). Three studies have investigated whether vitamin D_3 could benefit patients with CD, possibly through reducing intestinal inflammation. In one multicenter, double-blind, placebo-controlled study, the relapse rate in CD patients in remission after one year of treatment was significantly lower in those supplemented daily with 1,200 IU of vitamin D_3 and 1,200 mg of calcium compared to those who received calcium alone (13% vs. 29%) (325). In a second pilot study, incremental daily doses of vitamin D_3, from 1,000 IU up to 5,000 IU, were administrated over a 24-week period to 18 CD patients in order to achieve circulating 25-hydroxyvitamin D concentrations >40 ng/mL. Although half of the patients failed to achieve 40 ng/mL, the mean 25-hydroxyvitamin D concentration was raised to 45 ng/mL (from a baseline mean of 16 ng/mL), and the overall improvement in vitamin D status was associated with a significant decrease in disease severity as assessed by Crohn's Disease Activity (CDAI) scores (326). In a three-month, randomized, double-blind, placebo-controlled trial in 27 CD patients in remission, daily supplementation with vitamin D_3 (2,000 IU) improved vitamin D status but had no significant effect on intestinal permeability ('leaky gut') or measures of inflammation and disease activity (327). Yet, the study suggested that achieving serum 25-hydroxyvitamin D concentrations ≥30 ng/mL might help reduce intestinal inflammation and improve patients' quality of life. Additional studies are needed to confirm the therapeutic efficacy of vitamin D in inflammatory bowel diseases.

Cardiovascular disease

The prospective analysis of 41,504 electronic medical records in the Intermountain Heart Collaborative study found that only one-third of patients had adequate serum 25-hydroxyvitamin D concentrations (>30 ng/mL); vitamin D insufficiency (serum 25-hydroxyvitamin D concentrations ≤30 ng/mL) was associated with increased prevalence and incidence of many cardiovascular conditions, including hypertension, coronary artery disease, heart failure, and stroke (328). Suboptimal vitamin D status has also been linked to arterial stiffness and vascular endothelial dysfunction — strong determinants of incident hypertension and adverse cardiovascular outcomes (329).

Hypertension

Several intervention studies have evaluated the effect of vitamin D supplementation on blood pressure. An early controlled clinical trial in 18 men and women with untreated mild hypertension living in the Netherlands found that exposure to UVB radiation three times weekly for six weeks during the winter increased serum 25-hydroxyvitamin D concentrations by 162%, lowered PTH concentrations by 15%, and decreased 24-hour ambulatory systolic and diastolic blood pressure measurements by an average of 6 mm Hg (330). A recent meta-analysis of 16 randomized controlled trials involving 1,879 participants, either healthy or with pre-existing cardiometabolic conditions (including hypertension), found no significant reduction in systolic and diastolic blood pressures with vitamin D supplementation (800-8,571 IU/day for five weeks to one year). However, a subgroup analysis of six trials found a significant reduction of 1.31 mm Hg in diastolic blood pressure in individuals with preexisting conditions. While improvements in blood pressure may be expected in cases of vitamin D insufficiency/deficiency, the authors noted that suboptimal vitamin D status in participants was not exclusively observed in those with cardiometabolic conditions (331). In contrast, in two recent intervention studies — the Styrian vitamin D hypertension trial (332) and the Vitamin D therapy in individuals at high risk of hypertension trial [DAYLIGHT] (333) — subjects with (pre)hypertension supplemented with vitamin D_3 (400 to 4,000 IU/day for two to six months) showed no evidence of blood pressure lowering, regardless of their baseline vitamin D status (insufficient or adequate, according to the IOM's current cutoffs).

Conditions that decrease vitamin D synthesis in the skin, such as having dark-colored skin, living in temperate latitudes, and aging, are associated with increased prevalence of hypertension (334), suggesting that vitamin D may reduce blood pressure levels in selected groups of individuals. In the above-mentioned meta-analysis, one four-arm, double-blind, placebo-controlled clinical trial was conducted in 283 African Americans randomized to receive daily vitamin D_3 supplements of 1,000 IU, 2,000 IU, or 4,000 IU for a period of three months. Systolic blood pressure was decreased by 0.66 mm Hg with 1,000 IU/day, 3.4 mm Hg with 2,000 IU/day, and by 4 mm Hg with 4,000 IU/day while it increased by 1.7 mm Hg in the placebo group when compared to baseline. A significant reduction of 0.2 mm Hg in systolic blood pressure was detected per 1 ng/mL incremental increase in 25-hydroxyvitamin D concentration. However, there was no statistical difference on three-month change in blood pressure between vitamin D_3 and placebo (335). Another randomized, placebo-controlled study in 150 elderly participants (mean age, 77 years) showed that supplementation with 100,000 IU of vitamin D_3 every three months for one year did not significantly lower blood pressure compared to placebo (336).

Further research is needed to determine whether vitamin D supplementation is helpful in the prevention or management of hypertension.

Congestive heart failure

Congestive heart failure (also called cardiac insufficiency) is characterized by increased heart rate and subsequent hypertrophy of the left heart ventricle. Cardiac insufficiency is associated with a reduced left ventricular ejection fraction (LVEF), assessed by echocardiography. Inhibitors of angiotensin-converting enzyme (ACE) (see Blood pressure regulation) are currently used as first-line therapy for patients with heart failure. In a cross-sectional study in healthy patients who underwent coronary angiography, serum 25-hydroxyvitamin D concentrations <30 ng/mL were associated with poorer coronary flow rates (337). Suboptimal vitamin D status has also been linked to poorer prognosis in patients with heart failure (338). Over the past several years, a number of intervention studies have examined the effect of vitamin D supplementation in those with cardiac insufficiency. In a 12-week randomized, double-blind, placebo-controlled study, daily supplementation with 1,200 IU of vitamin D_3 in children with chronic congestive heart failure led to a significant increase in vitamin D status accompanied by an improved heart muscle performance (increased LVEF), as well as by lower levels of PTH and pro-inflammatory cytokines (339). In another randomized, double-blind, placebo-controlled trial in 64 elderly patients with heart failure, participants receiving 800 mg/day of calcium and 50,000 IU/week of vitamin D_3 did not perform significantly better at physical performance tasks (used as proxy to assess aerobic capacity and skeletal muscle strength) compared to those supplemented with calcium only (340). A recent meta-analysis of seven small randomized placebo-controlled trials in 573 subjects with heart failure showed that vitamin D supplementation (from 1,000 IU/day to 50,000 IU/week) for six weeks to nine months could reduce serum concentrations of PTH, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). Yet, there were no significant differences in LVEF, circulating interleukin-10 (IL-10) concentration, and renin concentration between patients treated with vitamin D and those given a placebo (341). Finally, in the EVITA (Effect of vitamin D on all-cause mortality) trial in patients with end-stage heart failure and inadequate vitamin D status (baseline serum 25-hydroxyvitamin D values, 8.6-19.7 ng/mL), supplementation with 4,000 IU/day for three years did not reduce the risk of mortality compared to placebo (342).

Sources

Sunlight

Solar ultraviolet-B radiation (UVB; wavelengths of 290 to 315 nanometers) stimulates the production of vitamin D_3 in the epidermis of the skin (343). Sunlight exposure can provide most people with their entire vitamin D requirement. Children and young adults who spend a short time outside two or three times a week will generally synthesize all the vitamin D they need to prevent deficiency. One study reported that serum vitamin D concentrations following exposure to one minimal erythemal dose of simulated sunlight (the amount required to cause a slight pinkness of the skin) to the whole body was equivalent to ingesting approximately 10,000 to 25,000 IU of vitamin D (344). People with dark-colored skin synthesize markedly less vitamin D on exposure to sunlight than those with lighter complexion (34). Additionally, older adults have diminished capacity to synthesize vitamin D from sunlight exposure and frequently use sunscreen or protective clothing in order to prevent skin cancer and sun damage. The application of sunscreen with an SPF factor of 10 reduces production of vitamin D by 90% (30). In latitudes around 40 degrees north or 40 degrees south (Boston is 42 degrees north), there is insufficient UVB radiation available for vitamin D synthesis from November to early March. Ten degrees farther north or south (Edmonton, Canada), the "vitamin D winter" extends from mid-October to mid-March. It has been estimated that up to 15 minutes of daily sun exposure on the hands, arms, and face around 12 pm throughout the year at 25 degrees latitude (Miami, FL) and during the spring, summer, and fall at 42 degrees (Boston, MA) latitude may provide a light-skinned individual with 1,000 IU of vitamin D (345).

Food sources

Vitamin D is found naturally in only a few foods, such as some fatty fish (mackerel, salmon, sardines), fish liver oils, eggs from hens that have been fed vitamin D, and mushrooms exposed to sunlight or UV light. In the US, milk and infant formula are fortified with vitamin D so that they contain 400 IU (10 μg) per quart. However, other dairy products, such as cheese and yogurt, are not always fortified with vitamin D. Some cereal, bread, and fruit juices may also be fortified with vitamin D. Accurate estimates of average dietary intakes of vitamin D are difficult because of the high variability of the vitamin D content of fortified foods (346). The vitamin D content (sum of vitamin D_2 and vitamin D_3) of some vitamin D-rich foods is listed in **Table 2** in both international units (IU) and micrograms (μg). For more information on the nutrient content of specific foods, search USDA's FoodData Central. The 25-hydroxyvitamin D metabolite is also present at low levels is certain foods, including meats, dairy products, and eggs (347, 348).

Table 2. Some Food Sources of Vitamin D

Food	Serving	Vitamin D (IU)	Vitamin D (μg)
Pink salmon, canned	3 ounces	465	11.6
Mackerel, canned (boneless)	3 ounces	248	6.2
Sardines, canned	3 ounces	164	4.1
Milk, low-fat (1%), fortified with vitamin D	8 fluid ounces	108	2.7
Orange juice, fortified with vitamin D	8 fluid ounces	100	2.5
Cereal, fortified	1 serving (usually 1 cup)	40-50	1.0-1.3
Egg yolk	1 large	37	0.9

Supplements

Most vitamin D supplements available without a prescription contain cholecalciferol (vitamin D_3). Multivitamin supplements generally provide 400 IU-1,000 IU (10 μg-25 μg) of vitamin D_2 or vitamin D_3. Single-ingredient vitamin D supplements may provide 400 to 50,000 IU of vitamin D_3, but 400 IU is the most commonly available dose (66). A number of calcium supplements may also provide vitamin D. A meta-analysis of randomized controlled trials suggested that bolus doses of vitamin D_2 (ergocalciferol) may not always be as effective as vitamin D_3 in raising serum 25-hydroxyvitamin D concentrations, yet no difference in efficacy was found with daily supplementation with vitamin D_2 or vitamin D_3 (349). Nonetheless, a 25-week, randomized, double-blind, placebo-controlled trial found daily supplementation with 1,000 IU of vitamin D_3 initiated at the end of summer to be more efficacious than vitamin D_2 in maintaining summertime concentrations of 25-hydroxyvitamin D during fall and winter months (350).

There is growing interest in using the hydroxylated form of cholecalciferol, 25-hydroxyvitamin D_3 (calcidiol; calcifediol), as a supplement. This vitamin D metabolite is synthesized by the liver of humans and animals from cholecalciferol produced in skin or consumed in the diet, and is present in some foods (e.g., meats, milk, eggs) at low levels (347, 348). In general, clinical studies have found calcifediol is two to five times more potent at increasing blood concentrations of 25-hydroxyvitamin D compared to supplementation with equivalent doses of cholecalciferol (351-359). Supplementation with calcifediol may thus represent a means to improve vitamin D status rapidly and consistently with lower doses than cholecalciferol and may benefit those individuals with conditions that decrease intestinal absorption of cholecalciferol (359). However, the 25-hydroxyvitamin D_3 form is presently not available as an over-the-counter supplement in the United States.

Safety

Toxicity

Vitamin D toxicity (hypervitaminosis D) has not been observed to result from sun exposure. The reason is that excessive sunlight exposure generates a number of biologically inert photoproducts from 7-dehydrocholesterol and cholecalciferol (3). Vitamin D toxicity induces abnormally high serum calcium concentration (hypercalcemia), which could result in bone loss, kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. Hypercalcemia has been observed following daily doses of greater than 50,000 IU of vitamin D (360). Overall, research suggests that vitamin D toxicity is very unlikely in healthy people at intake levels lower than 10,000 IU/day (361-363). However, the Food and Nutrition Board of the IOM conservatively set the tolerable upper intake level (UL) at 4,000 IU/day (100 μg/day) for all adults (**Table 3**). Certain medical conditions can increase the risk of hypercalcemia in response to vitamin D, including primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma (361). People with these conditions may develop hypercalcemia in response to any increase in vitamin D nutrition and should consult a qualified health care provider regarding any increase in vitamin D intake.

Table 3. Tolerable Upper Intake Level (UL) for Vitamin D

Age Group	μg/day	IU/day
Infants 0-6 months	25	1,000
Infants 6-12 months	37.5	1,500
Children 1-3 years	62.5	2,500
Children 4-8 years	75	3,000
Children 9-13 years	100	4,000
Adolescents 14-18 years	100	4,000
Adults 19 years and older	100	4,000

Drug interactions

The following medications should not be taken at the same time as vitamin D because they can decrease the intestinal absorption of vitamin D: cholestyramine (Questran), colestipol (Colestid), orlistat (Xenical), and mineral oil (364, 365). The following medications increase the metabolism of vitamin D and may decrease serum 25-hydroxyvitamin D concentrations: phenytoin (Dilantin), fosphenytoin (Cerebyx), phenobarbital (Luminal), carbamazepine (Tegretol), and rifampin (Rimactane) (6). Cimetidine, a H_2 blocker that suppresses stomach acid secretion, inhibits the hydroxylation of vitamin D in the liver (366). Treating acid reflux, gastroesophageal reflux disease (GERD), or ulcers with proton-pump inhibitors (omeprazole, lansoprazole) might interfere with calcium absorption and increase the risk of fracture such that patients are advised to take calcium and vitamin D supplements (367). The oral antifungal medication, ketoconazole, inhibits the 25-hydroxyvitamin D_3-1α-hydroxylase enzyme and has been found to reduce serum 1α,25-dihydroxyvitamin D concentrations in healthy men (368). The Endocrine Society also recommends monitoring vitamin D status of patients on glucocorticoids and HIV treatment drugs because these medications increase the catabolism of 25-hydroxyvitamin D (40). The use of some cytostatic agents (cell growth inhibitors) may also increase the degradation of 25-hydroxyvitamin D and 1α,25-dihydroxyvitamin D in cancer patients under chemotherapy (6). The induction of hypercalcemia by toxic levels of vitamin D may precipitate cardiac arrhythmia in patients on digoxin (Lanoxin) (366). Hypercalcemia may also reduce the effectiveness of verapamil (Calan) and diltiazem (Cardizem) in atrial fibrillation (366).

Linus Pauling Institute Recommendation

The Linus Pauling Institute recommends that generally healthy adults take 2,000 IU (50 μg) of supplemental vitamin D daily. Most multivitamins contain 400 IU (10 μg) of vitamin D, and single-ingredient vitamin D supplements are available for additional supplementation. Sun exposure, diet, skin color, and body mass index (BMI) have variable, substantial impact on body vitamin D levels. To adjust for individual differences and ensure adequate body vitamin D status, the Linus Pauling Institute recommends aiming for a serum 25-hydroxyvitamin D concentration of at least 30 ng/mL (75 nmol/L). Observational studies suggest that serum 25-hydroxyvitamin D concentrations between 30 ng/mL and 60 ng/mL are associated with lower risks of adverse health outcomes, including cancers and autoimmune diseases.

The American Academy of Pediatrics currently suggests that all infants, children, and adolescents receive 400 IU of supplemental vitamin D daily (19). Consistent with the recommendations of the Endocrine Society (40), the Linus Pauling Institute recommends daily intakes of 400 to 1,000 IU (10 to 25 μg) of vitamin D in infants and 600 to 1,000 IU (15 to 25 μg) of vitamin D in children and adolescents. Given the average vitamin D content of breast milk, infant formula, and the diets of children and adolescents, supplementation may be necessary to meet these recommendations.

Older adults (>50 years)

Daily supplementation with 2,000 IU (50 μg) of vitamin D is especially important for older adults because aging is associated with a reduced capacity to synthesize vitamin D in the skin upon sun exposure.

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Vitamin E

Contents

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Read the Nutrition Information Brief on vitamin E by Maret G. Traber, Ph.D.

Summary

- Naturally occurring vitamin E includes eight fat-soluble isoforms: α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. Yet, the body preferentially uses α-tocopherol, and only α-tocopherol supplementation can reverse vitamin E deficiency symptoms. *(More information)*
- α-Tocopherol functions as a chain-breaking antioxidant, preventing the propagation of free radicals in membranes and plasma lipoproteins. α-Tocopherol is also likely involved in strengthening certain aspects of cell-mediated immunity. *(More information)*
- Vitamin E deficiency can be caused by fat malabsorption disorders or by genetic abnormalities that affect vitamin E transport. Severe deficiency symptoms include vitamin E deficiency-induced ataxia, peripheral neuropathy, muscle weakness, and damage to the retina of the eye. *(More information)*
- The current recommended dietary allowance (RDA) is 15 mg/day of α-tocopherol. It is estimated that more than 90% of Americans adults do not meet the estimated average requirement (EAR) of 12 mg/day of α-tocopherol. *(More information)*
- Randomized controlled trials investigating primary and/or secondary prevention of chronic diseases, such as cardiovascular disease, cancer, and cataracts, do not currently support a preventative effect of supplemental α-tocopherol. *(More information)*
- Limited clinical evidence suggests that vitamin E supplementation may be beneficial for managing age-related macular degeneration and

- Disease Treatment
    - Age-related macular degeneration
    - Type 2 diabetes mellitus
    - Fatty liver diseases
    - Cognitive deterioration and Alzheimer's disease
- Sources
    - Food
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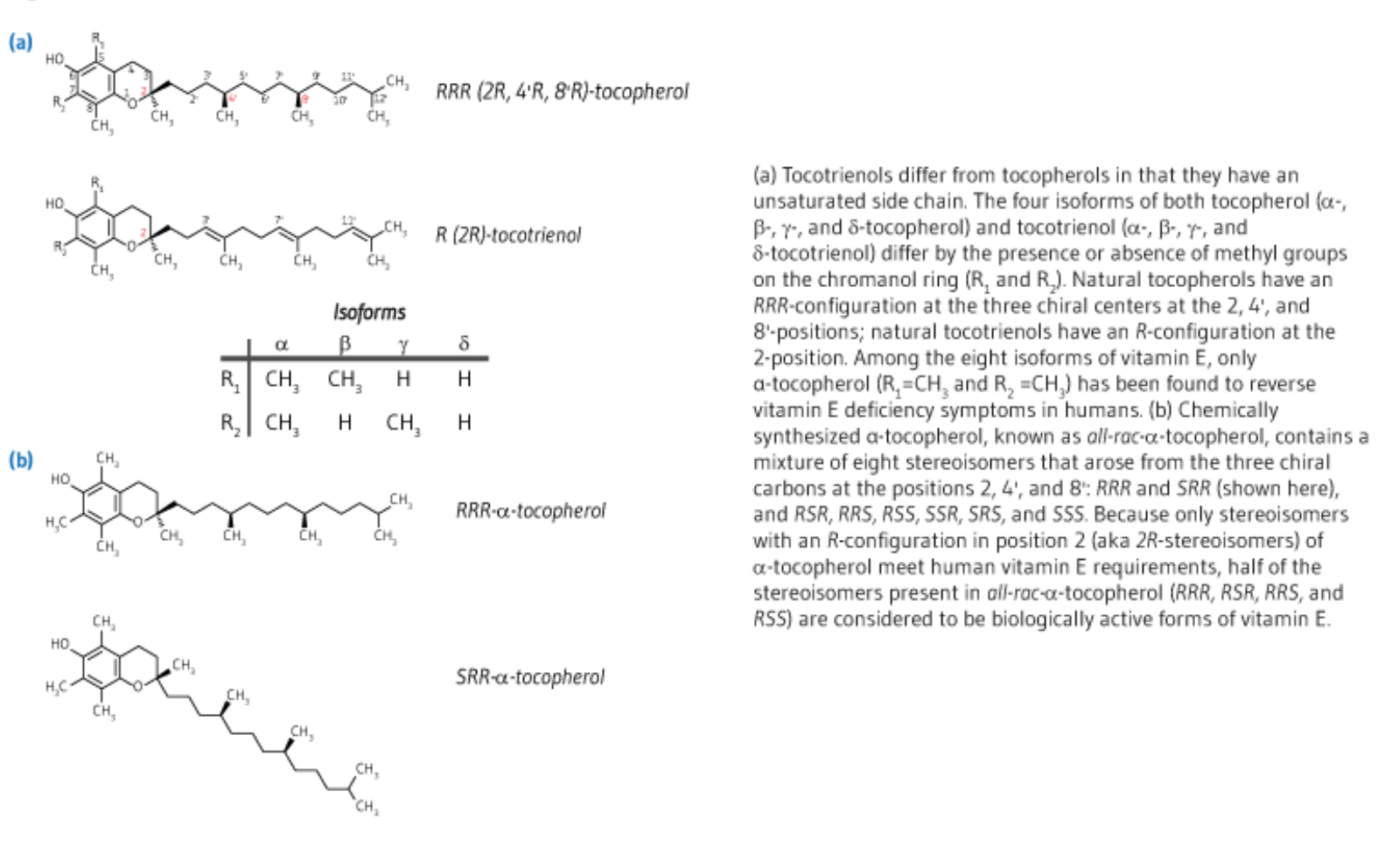
fatty liver diseases secondary to type 2 diabetes mellitus. *(More information)*

- Supplementation with α-tocopherol was found to slow cognitive decline or loss of functional abilities in cognitively impaired subjects in some, but not all, clinical studies. *(More information)*
- Plant seeds, especially sunflower seeds, almonds, and hazelnuts, are rich sources of α-tocopherol such that many vegetable oils (e.g., olive oil and canola oil) also contain α-tocopherol. Other sources include tomato, avocado, spinach, asparagus, Swiss chard, and broccoli. *(More information)*
- High doses of supplemental α-tocopherol may interfere with the vitamin K-dependent blood clotting cascade and increase the risk of bleeding in individuals taking anticoagulant drugs. A tolerable upper intake level (UL) for α-tocopherol in adults is set at 1,000 mg/day and applies to all possible stereoisomers of α-tocopherol. *(More information)*

The term vitamin E describes a family of eight fat-soluble molecules with antioxidant activities: four tocopherol isoforms (α-, β-, γ-, and δ-tocopherol) and four tocotrienol isoforms (α-, β-, γ-, and δ-tocotrienol) (**Figure 1**). Only one form, α-tocopherol, meets human vitamin E requirements (see The RDA). In the human liver, α-tocopherol is the form of vitamin E that is preferentially bound to α-tocopherol transfer protein (α-TTP) and incorporated into lipoproteins that transport α-tocopherol in the blood for delivery to extrahepatic tissues. Therefore, it is the predominant form of vitamin E found in the blood and tissues (1). In addition, α-tocopherol appears to be the form of vitamin E with the greatest nutritional significance, such that it will be the primary topic of the following discussion.

Figure 1. Chemical Structures of Vitamin E Isoforms



(a) Tocotrienols differ from tocopherols in that they have an unsaturated side chain. The four isoforms of both tocopherol (α-, β-, γ-, and δ-tocopherol) and tocotrienol (α-, β-, γ-, and δ-tocotrienol) differ by the presence or absence of methyl groups on the chromanol ring (R_1 and R_2). Natural tocopherols have an *RRR*-configuration at the three chiral centers at the 2, 4', and 8'-positions; natural tocotrienols have an *R*-configuration at the 2-position. Among the eight isoforms of vitamin E, only α-tocopherol (R_1=CH_3 and R_2 =CH_3) has been found to reverse vitamin E deficiency symptoms in humans. (b) Chemically synthesized α-tocopherol, known as *all-rac*-α-tocopherol, contains a mixture of eight stereoisomers that arose from the three chiral carbons at the positions 2, 4', and 8': *RRR* and *SRR* (shown here), and *RSR, RRS, RSS, SSR, SRS*, and *SSS*. Because only stereoisomers with an *R*-configuration in position 2 (aka *2R*-stereoisomers) of α-tocopherol meet human vitamin E requirements, half of the stereoisomers present in *all-rac*-α-tocopherol (*RRR, RSR, RRS*, and *RSS*) are considered to be biologically active forms of vitamin E.

[Figure 1 - Click to Enlarge]

Function

α-Tocopherol

Natural versus synthetic α-tocopherol

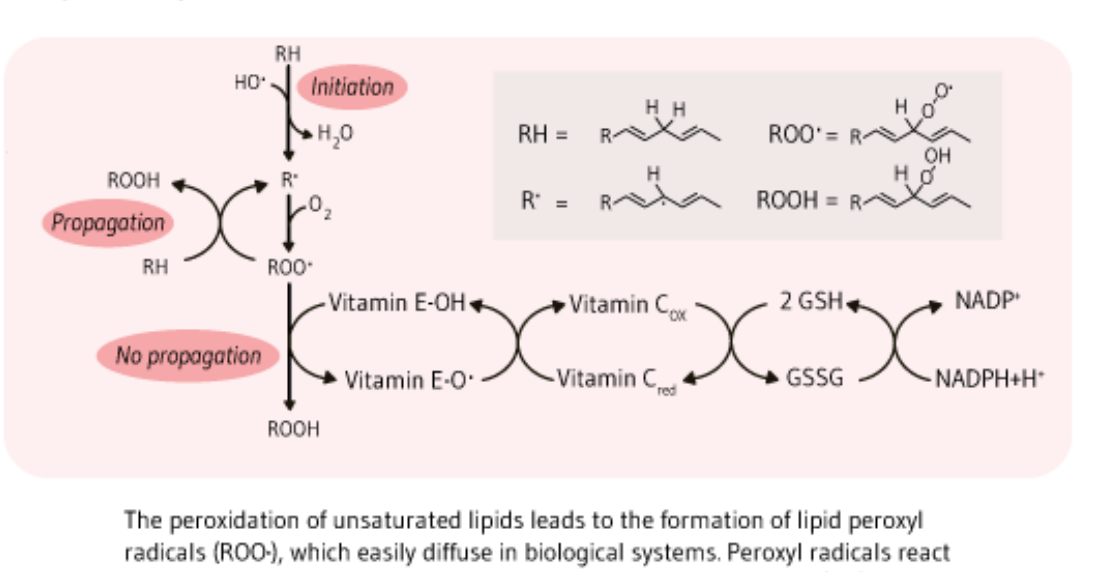
Natural α-tocopherol made by plants found in food has an *RRR*-configuration at the 2, 4', and 8'-position of the α-tocopherol molecule (wrongly referred to as *d*-α-tocopherol) (see **Figure 1**). Chemically synthesized *all-rac*-α-tocopherol (*all-racemic*-α-tocopherol; incorrectly labeled *dl*-α-tocopherol) is a mixture of eight stereoisomers of α-tocopherol, which arose from the three chiral carbons at the 2, 4', and 8'-positions: *RRR*-, *RSR*-, *RRS*-, *RSS*-, *SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol (see **Figure 1**). While all stereoisomers have equal *in vitro* antioxidant activity, only the forms in the *R*-conformation at position 2 (noted 2*R*) meet the vitamin E requirements in humans (2).

Antioxidant activity

The main function of α-tocopherol in humans is that of a fat-soluble antioxidant. Fats, which are an integral part of all cell membranes, are vulnerable to damage through lipid peroxidation by free radicals. α-Tocopherol is uniquely suited to intercept peroxyl radicals and thus prevent a chain reaction of lipid oxidation (**Figure 2**). When a molecule of α-tocopherol neutralizes a free radical, it is oxidized and its antioxidant capacity is lost. Other antioxidants, such as vitamin C, are capable of regenerating the antioxidant capacity of α-tocopherol (**Figure 2**) (reviewed in 1).

Aside from maintaining the integrity of cell membranes throughout the body, α-tocopherol protects the fats in low-density lipoproteins (LDLs) from oxidation. Lipoproteins are particles composed of lipids and proteins that transport fats through the bloodstream. LDLs specifically transport cholesterol from the liver to the tissues of the body. Oxidized LDLs have been implicated in the development of cardiovascular disease (3).

Figure 2. Antioxidant Activity of α-Tocopherol



The peroxidation of unsaturated lipids leads to the formation of lipid peroxyl radicals (ROO•), which easily diffuse in biological systems. Peroxyl radicals react 1,000 times faster with α-tocopherol than with unsaturated lipids (RH). The hydroxyl group in the chromanol head of α-tocopherol can donate hydrogen to scavenge lipid peroxyl radicals, which halts their propagation in membranes and circulating lipoproteins. The presence of other antioxidants, such as vitamin C (ascorbate), is required to regenerate the antioxidant capacity of α-tocopherol. *GSSH, oxidized glutathione; GSH, reduced glutathione, NADP, nicotinamide adenine diphosphate; NADPH, reduced NADP; RH, unsaturated lipid; R•, lipid (carbon-centered) radical; ROO•,* hydroperoxide; Vitamin E-OH, α-tocopherol (reduced form); *Vitamin E-O•, tocopheroxyl radical (oxidized form); Vitamin* C_{ox}*, dehydroascorbate (oxidized vitamin C); Vitamin* C_{red}*, ascorbate (reduced vitamin C).*

[Figure 2 - Click to Enlarge]

Effects on cell-mediated immunity

Other functions of α-tocopherol are likely to be related to its antioxidant capacity (1). For instance, α-tocopherol can protect the physiological properties of lipid bilayer membranes and may influence the activity of membrane proteins and enzymes (4). In cell culture studies, α-tocopherol was found to improve the formation of an adhesive junction (known as immune synapse) between naïve T lymphocytes and antigen-presenting cells (APC), which eventually prompted T cell activation and proliferation (see Disease Prevention) (5, 6).

γ-Tocopherol and tocotrienols

Vitamin E forms other than α-tocopherol are also known to be potent antioxidants. Tocotrienols and γ-tocopherol are thought to be better scavengers of peroxyl radicals and reactive nitrogen species, respectively, than α-tocopherol (7). Yet, in the body, (1) α-tocopherol is preferentially retained in the liver by the binding to α-tocopherol transfer protein (α-TTP), which incorporates α-tocopherol into lipoproteins for delivery to extrahepatic tissues; and (2) forms of vitamin E other than α-tocopherol are actively metabolized and excreted. Hence, while γ-tocopherol is the most common form of vitamin E in the American diet (8), its plasma and tissue concentrations are generally significantly lower than those of α-tocopherol, and more γ-tocopherol is excreted in urine than α-tocopherol, suggesting less γ-tocopherol is needed for use by the body (1).

Studies conducted *in vitro* and in animals have indicated that γ-tocopherol and its major metabolite, γ-carboxyethyl hydroxychroman (γ-CEHC), may play a role in protecting the body from free radical-induced damage in various conditions of oxidative stress and inflammation (reviewed in 7). Limited intervention studies (highlighted in 7) have not convincingly demonstrated a potential anti-inflammatory effect of γ-tocopherol in humans. Yet, in two recent randomized, placebo-controlled studies, the supplementation of smokers with γ-tocopherol potentiated short-term benefits of smoking cessation (with or without nicotine replacement therapy) on vascular endothelial function (9, 10).

Numerous preclinical studies have also suggested that tocotrienols might be beneficial in the prevention of chronic diseases (11). For instance, tocotrienols (especially δ-tocotrienol) have shown greater anti-proliferative and pro-apoptotic effects than tocopherols in malignant cell lines (12). However, a number of factors, including dose, formulation, and type of study population, affect the bioavailability of tocotrienols and may undermine their putative efficacy in humans (13). There are currently no data available on the effectiveness of supplemental tocotrienols in humans (11).

Nutrient interactions

Dietary and circulating fatty acids

The mechanism of vitamin E digestion and uptake into intestinal cells (enterocytes) is unclear but requires bile acids and pancreatic enzymes, and the packaging along with dietary fat into chylomicrons. The efficiency of vitamin E absorption increases with the amount of fat in ingested food, such that vitamin E absorption from supplements is likely to be minimal with low-fat meals (14, 15).

In the circulation, all lipoproteins (i.e., VLDLs, LDLs, and HDLs) are involved in the transport and tissue distribution of α-tocopherol (1). Increased concentrations of lipids (cholesterol and triglycerides) in the blood have been correlated to higher serum α-tocopherol concentrations. However, if a high blood concentration of lipids is associated with a slower turnover of lipoproteins, then the distribution of α-tocopherol to tissues may be substantially altered (16).

Vitamin C

A few human studies using conditions of oxidative stress have demonstrated the importance of vitamin C (ascorbic acid) in the recycling of oxidized α-tocopherol back to its reduced state (see **Figure 2**). Oxidative stress caused by cigarette smoking accelerates the depletion of plasma α-tocopherol in smokers compared to nonsmokers (17). In a double-blind, placebo-controlled trial in 11 smokers and 13 nonsmokers given α-tocopherol and γ-tocopherol that was labeled with deuterium (hence traceable), supplementation with vitamin C reduced the rate of vitamin E loss in plasma, most probably by regenerating tocopheryl radicals back to nonoxidized forms (18).

Vitamin K

One study in adults with normal coagulation (clotting) status found that daily supplementation with 1,000 IU (670 mg) of *RRR*-α-tocopherol for 12 weeks decreased γ-carboxylation of prothrombin, a vitamin K-dependent factor in the coagulation cascade (19). Individuals taking anticoagulant drugs like warfarin and those who are vitamin K deficient should not take vitamin E supplements without medical supervision because of the increased risk of bleeding (see Safety) (20).

Deficiency

Causes

Severe vitamin E deficiency rarely occurs in humans but has been observed as a result of malnutrition (21). Severe vitamin E deficiency has been associated with specific genetic defects affecting the transport of α-tocopherol by α-tocopherol transfer protein (α-TTP) and lipoproteins. Vitamin E deficiency has also been observed in individuals with fat malabsorption syndromes, which impair the absorption of dietary fats and therefore fat-soluble vitamins like vitamin E (see Nutrient interactions) (21).

Symptoms

Severe vitamin E deficiency results mainly in neurologic symptoms, including impaired balance and coordination (spinocerebellar ataxia), injury to the sensory nerves (peripheral neuropathy), muscle weakness (myopathy), and damage to the retina of the eye (retinopathy). For this reason, people who develop peripheral neuropathy, ataxia, or retinitis pigmentosa (RP) of unknown causes should be screened for vitamin E deficiency (21). The results of one randomized controlled trial in 601 patients with common forms of RP indicated that daily supplementation with 400 IU of *all-rac*-α-tocopherol (180 mg of *RRR*-α-tocopherol) modestly but significantly increased the loss of retinal function (22). In contrast, daily supplementation with 15,000 IU of vitamin A (4,500 μg RAE) significantly slowed the loss of retinal function over a period of four to six years, suggesting that patients with common forms of RP may benefit from long-term vitamin A supplementation but should avoid high-dose supplemental vitamin E.

Inherited defects in α-TTP are associated with a characteristic syndrome called AVED (Ataxia with Vitamin E Deficiency). A recent case study reported that visual impairment in a middle-age patient with AVED was caused by both RP and early-onset macular degeneration (23). Supplementation with high-dose vitamin E (800-1,200 mg/day) is used to prevent neurologic deterioration in AVED subjects (21).

Moreover, the developing nervous system appears to be especially vulnerable to vitamin E deficiency. For instance, children with severe vitamin E deficiency at birth rapidly experience irreversible neurologic symptoms if not treated with vitamin E. In contrast, individuals who develop gastrointestinal disorders affecting vitamin E absorption in adulthood may not develop neurologic symptoms for 10-20 years (21). It should also be noted that neurologic symptoms caused by vitamin E deficiency have not been reported in healthy individuals who consume diets low in vitamin E.

Marginal deficiency

Although frank vitamin E deficiency is rare, marginal intake of vitamin E is relatively common. Between 1988 and 1994, the US National Health and Nutrition Examination Survey III (NHANES III) examined the dietary intake and blood concentrations of α-tocopherol in 16,295 adults. The study reported that about one-third of all participants had blood concentrations of α-tocopherol below 20 micromoles/liter (μmol/L) — a cutoff value chosen because of its initial association with an increased risk for cardiovascular disease (24). More recent data from 18,063 participants in NHANES 2003-2006 indicated an average dietary intake of α-tocopherol from food (including enriched and fortified sources) among Americans adults of 7.2 mg/day (25). This intake is well below the current recommended dietary allowance of 15 mg/day (see the RDA). At this level of dietary intake, more than 93% of American adults do not meet the estimated average requirement (EAR) of 12 mg/day for vitamin E (25). In addition, a recent nested case-control study in Bangladeshi women suggested that inadequate vitamin E status during early pregnancy may be associated with an increased risk of miscarriage (26).

Cigarette smoking is thought to increase the utilization of α-tocopherol such that smokers might be at increased risk of deficiency compared with nonsmokers (17). Also, the 19-year follow-up analysis of the Alpha-Tocopherol, Beta-Carotene cancer (ATBC) trial in older, male smokers indicated that participants in the highest versus lowest quintile of serum α-tocopherol concentrations (>31 μmol/L vs. <23 μmol/L) at baseline had reduced risks of total and cause-specific mortality (27).

It is not known whether marginal vitamin E deficiency increases the risk of chronic disease (1).

The Recommended Dietary Allowance (RDA)

The RDA for vitamin E was last revised by the Food and Nutrition Board of the US Institute of Medicine in 2000 (**Table 1**) (2). The RDA is based largely on the results of studies done in the 1950s in men fed vitamin E-deficient diets. In a test-tube analysis, vitamin E suppresses the breakdown of red blood cells (known as hemolysis) induced by hydrogen peroxide. Because hemolysis has also been reported in children with severe vitamin E deficiency, the preventive effect of vitamin E against oxidative damage-induced hemolysis was considered to be a clinically relevant *in vitro* analysis to assess vitamin E status. Importantly, this means that the latest RDA for vitamin E continues to be based on the prevention of deficiency symptoms rather than on health promotion and prevention of chronic disease.

The forms of α-tocopherol that meet the recommended intakes are *RRR*-α-tocopherol — the only naturally occurring form of vitamin E — and the three synthetic isomers, *RRS*-, *RSR*-, and *RSS*-α-tocopherol, which are found in nutritional supplements and fortified food.

Table 1 lists the RDA for α-tocopherol expressed in both milligrams (mg) and international units (IU).

Table 1. Recommended Dietary Allowance (RDA) for α-Tocopherol$^{*\#}$

Life Stage	Age	Males		Females	
		mg/day	IU/day	mg/day	IU/day
Infants (AI)	0-6 months	4	6	4	6
Infants (AI)	7-12 months	5	7.5	5	7.5
Children	1-3 years	6	9	6	9
Children	4-8 years	7	10.5	7.5	10.5
Children	9-13 years	11	16.5	11	16.5
Adolescents	14-18 years	15	22.5	15	22.5
Adults	19 years and older	15	22.5	15	22.5
Pregnancy	all ages	-	-	15	22.5
Breast-feeding	all ages	-	-	19	28.5

*These recommended intakes are limited to 2*R*-stereoisomeric forms of α-tocopherol.

$^{\#}$One mg of 2*R*-α-tocopherol is equivalent to 1.5 IU, and one IU is equivalent to 0.67 mg of 2*R*-α-tocopherol.

Disease Prevention

Age-related deterioration of immune function

The natural age-related decline of the immune function is accompanied by an increased susceptibility to infections, a poorer response to immunization, and higher risks of developing cancers and autoimmune diseases. α-Tocopherol has been shown to enhance specifically the T cell-mediated immune response that declines with advancing age (reviewed in 28). T cell impaired response has been partly associated with a reduced capacity of naïve T cells to be activated during antigen presentation, and to produce interleukin-2 (IL-2) and proliferate as a result (6). However, very few studies have addressed the potential association between α-tocopherol and immune function in humans (28). In a small intervention study in older adults (mean age, 70 years), supplementation with 200 mg/day of *all-rac*-α-tocopherol (equivalent to 100 mg of *RRR*-α-tocopherol) for three months significantly improved natural killer (NK) cytotoxic activity, neutrophil chemotaxis, phagocytic response, and enhanced mitogen-induced lymphocyte proliferation and interleukin-2 (IL-2) production compared to baseline (29). In an earlier trial, daily supplementation of healthy older adults (≥65 years of age) with 200 mg of *all-rac*-α-tocopherol for 235 days also improved T lymphocyte-mediated immunity — as measured with the delayed-type hypersensitivity (DTH) skin test — and increased the production of antibodies in response to hepatitis B and tetanus vaccines (30).

Lower α-tocopherol doses failed to improve the DTH response compared to a placebo in another study in healthy participants (ages, 65-80 years) (31). A randomized, placebo-controlled trial in 617 nursing home residents (≥65 years of age) reported that daily supplementation with 200 IU of synthetic α-tocopherol (90 mg of *RRR*-α-tocopherol) for one year significantly lowered the risk of contracting upper respiratory tract infections, especially the common cold, but had no effect on lower respiratory tract (lung) infections (32). More research is needed to examine whether supplemental vitamin E might enhance immune function and reduce risk of infection in older adults.

Cardiovascular disease

Primary prevention: in healthy adults

Observational studies: Results of several large observational studies in both men and women have suggested an inverse relationship between vitamin E consumption and risk of myocardial infarction or death from heart disease. Each study had a prospective design that measured vitamin E intake in generally healthy people who were followed over a period of time to determine the onset of cardiovascular events and analyze the association between the exposure and the outcome(s). In two of the studies, individuals who consumed more than 7 mg/day of dietary α-tocopherol were 35% less likely to die from heart disease than those who consumed less than 3-5 mg/day of α-tocopherol (33, 34). Two other large studies observed a significantly reduced risk of heart disease only in women and men who consumed at least 100 IU (67 mg)/day of supplemental *RRR*-α-tocopherol (35, 36).

Intervention studies: A randomized, placebo-controlled, intervention trial in 39,876 women (aged ≥45 years) participating in the Women's Health Study (WHS) found that supplementation with 600 IU (400 mg) of *RRR*-α-tocopherol every other day for 10 years resulted in a 34% reduction in nonfatal myocardial infarction and a 49% reduction in cardiovascular-related deaths but only in women aged at least 65 years at baseline (representing 10% of study participants) (37). Further analyses of WHS data showed that women in the vitamin E arm of the study experienced a 21% reduction in risk of venous thromboembolism (VTE) compared to placebo: the reduction was of 12% in women younger than 55 years old, 26% in women aged 65 years and older, and 44% in women with a history of VTE (38, 39). Another large randomized controlled trial — the Physicians' Health Study II (PHSII) — conducted in healthy middle-aged men found no significant effect of 400 IU of synthetic α-tocopherol (180 mg of *RRR*-α-tocopherol), given every other day for eight years, on the risk of major cardiovascular events in the entire cohort and in subgroup analyses (40). Besides, concerns were raised regarding a possible harmful effect of high-dose vitamin E supplementation on the risk of hemorrhagic stroke in this cohort (40).

Secondary prevention: in individuals with or at risk of cardiovascular disease

Conventional risk factors for cardiovascular disease (CVD) include cigarette smoking, physical inactivity, hypertension, dyslipidemia, and being overweight or obese. Other factors such as oxidative stress and inflammation are also thought to contribute to increasing CVD risk, especially in patients with chronic conditions like type 2 diabetes mellitus and chronic kidney disease. Although trials do not appear to support any cardiovascular benefit in healthy middle-aged and older subjects, vitamin E supplementation might help improve cardiovascular health and/or lower the risk of CVD in specific, higher risk subjects.

Observational studies: The presence of atherosclerotic plaques in arterial walls is one of the hallmarks of cardiovascular disease. Plaque rupture that causes blood clot formation is the usual cause of myocardial and cerebrovascular infarctions. The cross-sectional Asymptomatic Carotid Atherosclerosis Disease In Manfredonia (ACADIM) study in 640 at-risk individuals reported an inverse association between carotid intima-media thickness (CIMT) — a marker of atherosclerosis — and circulating concentrations of antioxidants, including vitamin E (41). However, other observational studies found no association between plasma vitamin E concentrations and CIMT (reviewed in 42).

Intervention studies: A small randomized controlled study assessing the effect of lipid-lowering drugs in men who had previously undergone a coronary artery bypass surgery found that the use of at least 100 IU/day (compared to less than 100 IU/day) of supplemental α-tocopherol (45 mg of *RRR*-α-tocopherol) was associated with reduced CIMT progression over a two-year period but only among participants in the placebo arm of the study (i.e., those who did not receive lipid-lowering drugs) (43). However, a recent meta-analysis of seven small placebo-controlled trials found little evidence that vitamin E supplementation may improve flow-mediated vascular dilation (FMD) of the brachial artery, a marker of vascular endothelial health that is adversely affected by CVD risk factors (44). In the Cambridge Heart AntiOxidant Study (CHAOS), a randomized, placebo-controlled intervention trial in 2,002 patients with coronary heart disease, daily supplementation with either 400 IU or 800 IU of synthetic α-tocopherol (180 mg or 360 mg of *RRR*-α-tocopherol) for a median 18 months dramatically reduced the occurrence of nonfatal myocardial infarctions by 77%. However, vitamin E supplementation did not significantly reduce total or cardiovascular-related deaths (45).

Another small trial in patients with renal failure — the Secondary Prevention with Antioxidants of cardiovascular disease in End-stage renal disease (SPACE) — found that supplementation with 800 IU (536 mg)/day of *RRR*-α-tocopherol for an average of 1.4 years significantly reduced the risk of myocardial infarction compared to placebo (46). A more recent randomized controlled study suggested that vitamin E supplementation may benefit a subgroup of patients with type 2 diabetes mellitus. The multicenter study by Milman et al. (47) was conducted in 1,434 type 2 diabetics (≥55 years old) carrying a specific variant of the haptoglobin protein (Hp), Hp2-2, which has a lower efficacy to bind and remove pro-oxidant, free hemoglobin from plasma, compared to Hp1-1 and Hp1-2 variants. The daily supplementation with 400 IU (268 mg) of *RRR*-α-tocopherol for 18 months resulted in a lower risk of myocardial infarction compared to placebo (47).

Other larger intervention trials conducted in cigarette smokers (the Alpha-Tocopherol, Beta-Carotene cancer prevention [ATBC] study (48)), in individuals at-risk of CVD (the Heart Outcomes Prevention Evaluation [HOPE]-The Ongoing Outcomes [HOPE-TOO study] (49)), or in patients who have suffered a myocardial infarction (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-GISSI-prevenzione trial (50)) failed to find significant CVD risk reductions with α-tocopherol supplementation. Besides, potentially harmful effects of supplemental vitamin E were reported on the risk of hemorrhagic stroke in the ATBC trial and on the risk of heart failure in the HOPE and GISSI trials (see Safety) (48-50).

Cancer

Oxidative damage to DNA by free radicals can lead to mutations that may contribute to causing cancer (51). Because of its ability to neutralize free radicals, vitamin E has been suggested to possess anticancer activity by protecting cells against oxidative damage. Yet, several large prospective cohort studies have failed to find significant associations between vitamin E intake and the incidence of lung or breast cancer (2). More recently, the VITamins And Lifestyle (VITAL) study prospectively assessed the association between long-term use of supplemental vitamins (10-year intake) and the risk of lung cancer in a cohort of 77,126 men and women (52). No relationships were reported between intake of multivitamins, vitamin C, vitamin E, or folate and the risk of lung cancer. However, the use of supplemental vitamin E in current but not in former smokers was associated with an 11% increased risk of lung cancer for every 100 mg/day increase, and intakes greater than 215 mg/day were specifically linked to a 29% increase in risk for non-small cell lung cancer (52).

To date, most clinical trials have failed to find any beneficial effects of vitamin E supplementation on the risk of various cancers. A randomized, placebo-controlled trial (RCT) in 39,876 women participating in the Women's Health Study found that supplementation with 600 IU (400 mg) of *RRR*-α-tocopherol every other day for 10 years had no effect on overall cancer incidence, tissue-specific cancer incidence, or cancer-related deaths (37). Yet, the results of a few large randomized controlled trials have suggested that vitamin E supplementation might affect the risk of prostate cancer. The Alpha-Tocopherol, Beta-Carotene cancer (ATBC) prevention study was a four-arm, randomized, double-blind, placebo-controlled trial designed to investigate the effect of α-tocopherol supplementation on lung cancer development in 29,133 male smokers. The study found a 32% reduction in the incidence of prostate cancer in participants given daily supplements of 50 mg of synthetic α-tocopherol (equivalent to 25 mg of *RRR*-α-tocopherol) alone or in combination with β-carotene compared to those given β-carotene alone or a placebo (53). However, no differences in the incidence of prostate cancer were found between α-tocopherol recipients and nonrecipients during the 18-year post-intervention period (54). In the Physicians' Health Study II (PHS II), which followed 14,641 healthy men aged 50 years and older, supplementation with 400 IU of synthetic vitamin E (equivalent to 180 mg of *RRR*-α-tocopherol) every other day for eight years had no effect on the risk of prostate cancer, other site-specific cancers, or total cancer (55). The supplementation of vitamin E (equivalent to 180 mg/day of *RRR*-α-tocopherol), alone or in combination with selenium, in the multicenter, randomized, placebo-controlled SELECT trial (SELenium and vitamin E Cancer prevention Trial) was halted because there was no evidence of benefit in preventing prostate cancer in 35,533 healthy men aged 50 years and older (56). After a median of seven years' follow-up, the risk of prostate cancer was found to be significantly increased by 17% in participants supplemented with vitamin E alone during the trial period — but not when vitamin E was combined with selenium — compared to placebo (57). A study of cases versus subcohort individuals drawn from the SELECT study assessed the effect of vitamin E and/or selenium supplementation on prostate cancer risk in relation to the selenium status of participants at baseline (58). Supplemental selenium with or without vitamin E was associated with a significant increase in the risk of advanced prostate cancer in individuals with higher versus lower selenium status. In addition, the risks of total and advanced prostate cancer were significantly elevated with vitamin E supplementation in subjects with low versus high selenium status (58). Recent investigations have suggested that sequence variations (polymorphisms) in vitamin E-related genes and genes coding for antioxidant enzymes, including selenoproteins, might modify the impact of high-dose vitamin E and selenium on the risk of prostate cancer (59-61).

Cataracts

Age-related cataracts appear to be the result of protein oxidation in the lens of the eye; antioxidants like α-tocopherol may protect the lens against oxidative damage from reactive oxygen species. In a recent cross-sectional study, vitamin E concentrations were found to be significantly lower in the lens and blood of subjects with age-related nuclear, but not cortical, cataracts when compared with an age-matched control group (62). However, earlier studies reported higher vitamin E concentrations in the lenses and blood of patients with cataracts (63, 64).

The results of several observational studies that examined the association between vitamin E consumption and the incidence or severity of cataracts are also mixed. Some reported that increased vitamin E intake protected against cataract development, while others found no association (65). Yet, a meta-analysis of eight studies, including 15,021 participants, found a 17% reduction in the risk of age-related cataract in subjects in the highest versus lowest quantile of dietary vitamin E intake (66). A recent prospective cohort study of 31,120 Swedish men followed for a mean of 8.4 years observed a greater risk of developing cataract in occasional and regular users of high-dose (about 100 mg/day) vitamin E supplements only, when compared with non-supplement users (67). However, the use of supplemental high-dose vitamin E with additional supplements or the use of low-dose vitamin E-containing multivitamin supplements was not found to be associated with an elevated cataract risk. A meta-analysis based on data from over 350,000 participants in 10 studies — including the above-cited study by Zheng Selin et al. (67) — found no association between supplemental vitamin E and risk of cataract (66).

In clinical settings, the supplementation of high-dose vitamin E — alone or in addition to other supplements — was found to be safe, yet the benefits regarding cataract risk or progression were limited. An early intervention trial found that a daily supplement of 50 mg of synthetic α-tocopherol (equivalent to 25 mg of *RRR*-α-tocopherol) did not alter the incidence of cataract surgery in male smokers (68). A randomized, placebo-controlled intervention trial in 4,629 men and women found that a daily antioxidant supplement containing 500 mg of vitamin C, 400 IU of *all-rac*-α-tocopheryl acetate (equivalent to 180 mg of *RRR*-α-tocopherol), and 15 mg of β-carotene did not affect development and progression of age-related cataracts over a seven-year period (69). Similarly, a four-armed, randomized, placebo-controlled study of 11,267 men from the Selenium and Vitamin E Cancer prevention trial (SELECT) failed to observe a reduction in cataract incidence with 400 IU/day of supplemental *all-rac*-α-tocopheryl acetate (180 mg/day of *RRR*-α-tocopherol), alone or in combination with selenium (200 μg/day), during a mean 5.6 years of follow-up (70). Daily antioxidant supplementation with 500 mg of vitamin C, 400 IU (268 mg) of *RRR*-α-tocopherol, and 15 mg of β-carotene did not limit the progression of cataract in a five-year intervention trial (71). Another four-year randomized, placebo-controlled trial reported that supplements containing 500 IU/day (335 mg/day) of *RRR*-α-tocopherol did not reduce the incidence or progression of cataract in older adults (72). Current available data from clinical trials do not support a preventative effect of vitamin E on cataracts.

Disease Treatment

Age-related macular degeneration

A recent pooled analysis of four randomized controlled trials in 62,520 subjects found that supplemental vitamin E or β-carotene did not reduce the risk of developing age-related macular degeneration (AMD), a multifactorial disease affecting the central area of the retina (73). However, a review of currently available data suggested that supplements of antioxidants plus zinc may reduce the progression of AMD and vision loss in affected individuals (74). The main evidence came from the Age-Related Eye Disease Study (AREDS). In this clinical trial, participants with borderline to advanced age-related macular degeneration (AMD) were randomized to receive (1) placebo; (2) antioxidant vitamins (15 mg/day of β-carotene, 500 mg/day of ascorbic acid, and 400 IU/day of *all-rac*-α-tocopheryl acetate); (3) zinc (80 mg/day) and copper (2 mg/day); or (4) both antioxidant vitamins and zinc and copper (75). The five-year results indicated that the risk of developing advanced AMD was significantly reduced in those taking zinc with or without antioxidant vitamins. Antioxidant vitamins alone failed to prevent the progression to advanced AMD, even in individuals at higher risk. It was concluded from this study that a combination of antioxidant vitamins and minerals may benefit people with intermediate AMD or advanced AMD in one eye (74, 76).

Type 2 diabetes mellitus

Oxidative stress contributes to the progression of type 2 diabetes mellitus and causes damage to many organs and tissues, including the pancreas, brain, eyes, peripheral nerves, and kidneys. Evidence from animal studies suggests that vitamin E supplementation could mitigate the role of oxidative damage in the occurrence of diabetes complications (reviewed in 77). In the Alpha-Tocopherol Beta-Carotene cancer prevention (ATBC) trial in male smokers, supplementation with 50 mg/day of synthetic α-tocopherol (25 mg/day of *RRR*-α-tocopherol) had no effect on the risk of incident type 2 diabetes mellitus during the 19-year post-intervention follow-up. Likewise, supplemental vitamin E intake during the trial made no difference on the incidence of macrovascular complications or mortality in participants with established type 2 diabetes (78). In addition, a meta-analysis of 14 heterogeneous randomized controlled trials, including 714 type 2 diabetic individuals, found that supplementation with vitamin E (200-1,800 IU/day for 6-27 weeks) had no effect on markers of glycemic control, including glycated hemoglobin A1c (HbA1c) level and measures of fasting glucose and fasting insulin concentrations (79). Further subgroup analyses indicated that higher doses of vitamin E (>400 IU/day) supplemented for longer periods (>12 weeks) significantly reduced HbA1c level and fasting insulin concentration, suggesting that vitamin E could possibly enhance insulin action and glucose disposal in type 2 diabetic individuals (79). Another recent meta-analysis of randomized controlled trials found that endothelial function in normal-weight and overweight — but not obese — patients with type 2 diabetes was significantly improved by supplementation with vitamin E and/or vitamin C (80). Although there is reason to suspect that vitamin E supplementation may have utility in the management of type 2 diabetes, evidence for benefit from large, well-controlled clinical trials is still lacking.

Fatty liver diseases

The increasing incidence of nonalcoholic fatty liver disease (NAFLD) in children and adults in industrialized countries is mainly attributed to the ongoing epidemic of obesity and type 2 diabetes mellitus. NAFLD results from the abnormal accumulation of fat (steatosis) in the liver in the absence of heavy alcohol consumption. Although the condition is considered to be largely benign, NAFLD can progress to a more severe disease called nonalcoholic steatohepatitis (NASH) with increased risks of cirrhosis, hepatocellular carcinoma (liver cancer), and cardiovascular disease (81). Oxidative stress is thought to be one of the possible mechanisms responsible for prompting inflammatory processes that can lead to the progression of NAFLD to NASH.

There is currently no established treatment for NAFLD and NASH other than interventions that encourage lifestyle changes and the use of medicines to control or treat metabolic disorders (82). In the multicenter PIVENS (PIoglitazone versus Vitamin E versus placebo for the treatment of Nonalcoholic Steatohepatitis) trial, 247 nondiabetic subjects with NASH were randomized to receive 30 mg/day of pioglitazone (an insulin-sensitizing drug), 800 IU/day (536 mg/day) of *RRR*-α-tocopherol, or a placebo for 96 weeks (83). Only vitamin E supplementation significantly increased the overall rate of improvement in histological abnormalities that characterize NASH on liver biopsies (i.e., hepatocellular ballooning, steatosis, and lobular inflammation) (84). Both active treatments improved some markers of liver function (i.e., alanine aminotransferase and aspartate aminotransferase) (84). Yet, results from another two-year, randomized controlled trial — called TONIC for Treatment Of Nonalcoholic fatty liver disease In Children — in 173 children (ages, 8-17 years) with NAFLD failed to observe any significant reduction in blood concentrations of alanine and aspartate aminotransferases either with supplemental vitamin E (536 mg/day of *RRR*-α-tocopherol) or with metformin (an anti-diabetic drug; 1,000 mg/day) compared to placebo (85). However, vitamin E supplementation significantly improved the overall disease activity score — used to quantify the severity of the disease. In addition, a recent meta-analysis of another six trials found that vitamin E significantly lowered circulating aminotransferase concentrations in NAFLD and NASH patients, suggesting liver function improvements (86). Finally, in a small nonrandomized, unblinded, controlled study in 42 obese children (mean age, 8 years) with NAFLD, lifestyle recommendations combined with 600 mg/day of supplemental *RRR*-α-tocopheryl acetate for six months reduced markers of oxidative stress and liver dysfunction and improved insulin sensitivity and the profile of lipid in the blood, when compared to baseline. No such changes in markers of oxidative stress, liver function, and glucose utilization were reported in the lifestyle intervention only group (87). Further randomized and well-controlled studies are needed to confirm these preliminary findings.

Cognitive deterioration and Alzheimer's disease

Mitochondrial dysfunction and oxidative stress are thought to contribute to the onset and/or progression of several neurodegenerative diseases, especially Alzheimer's disease (AD) (88). The progressive degeneration of neuronal cells that accompanies the decline of memory and other cognitive functions in subjects with Alzheimer's disease is associated with an intracellular aggregation of Tau fibrils, an extraneuronal accumulation of β-amyloid peptides into senile plaques, and an oxidation-reduction (redox) imbalance of complex etiology. In the brain of patients with mild cognitive impairment (MCI) and those with AD, the level of markers of oxidative damage to DNA, proteins, and lipids is increased, while the expression and activities of glutathione and antioxidant enzymes are reduced (reviewed in 88). In addition, a recent meta-analysis reported that circulating concentrations of vitamins, including vitamin A, vitamin C, and vitamin E, were significantly lower in AD patients than in cognitively healthy individuals (89). Other studies have documented low concentrations of vitamin E in cerebrospinal fluid of cognitively impaired patients (reviewed in 90).

Because a reduction in oxidative stress may help maintain cognitive status and/or prevent deterioration, the effects of vitamin E supplementation have been assessed in a few intervention studies. An early multicenter, randomized, placebo-controlled study in individuals with AD of moderate severity found that supplementation with 2,000 IU/day of *all-rac*-α-tocopherol (equivalent to 900 mg/day of *RRR*-α-tocopherol) for two years significantly delayed cognitive decline, slowed disease progression, and increased median survival (91). However, a placebo-controlled trial in 769 patients with MCI found that the same dosage of vitamin E did not affect the probability of progression from MCI to AD over a three-year period (92). In another double-blind, placebo-controlled trial, an improvement in cognitive performance — measured by the Mini Mental State Examination (MMSE) scoring system — was reported in AD patients randomized to receive 800 IU/day of *all-rac*-α-tocopherol (360 mg/day of *RRR*-α-tocopherol) for six months only when the treatment effectively reduced oxidative stress (as assessed by the measure of total glutathione and markers of lipid peroxidation in the blood) (93). Conversely, a failure to reduce oxidative stress resulted in supplemental vitamin E being more detrimental to the cognitive function of AD patients than placebo. In the most recent multicenter, randomized, double-blind, placebo-controlled study, supplemental vitamin E (2,000 IU/day; form of vitamin E not mentioned in the publication) for over two years significantly delayed functional decline — determined by the (in)ability to perform basic activities of daily living — and reduced the annual mortality rate in mild and moderate AD patients (94). Yet, vitamin E failed to affect cognitive performance measured with MMSE scores and other cognitive ability tests.

While there is currently little evidence to suggest that long-term supplementation of vitamin E provides any cognitive benefits in healthy older adults (95), additional research needs to confirm whether vitamin E supplementation could benefit the management of patients with mild-to-moderate cognitive impairments.

Sources

Food sources

Major sources of α-tocopherol in the American diet include vegetable oils (olive, sunflower, and safflower oils), nuts, whole grains, and green leafy vegetables. All eight forms of vitamin E (α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols) occur naturally in mostly plant-based foods but in varying amounts. **Table 2** lists the content of α-tocopherol and γ-tocopherol (in milligrams) in some rich sources of vitamin E. For more information on the vitamin E content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin E

Food	Serving	α-Tocopherol (mg)	γ-Tocopherol (mg)
Sunflower oil	1 tablespoon	5.6	0.6
Safflower oil	1 tablespoon	4.6	-
Grapeseed oil	1 tablespoon	3.9	-
Canola oil	1 tablespoon	2.4	3.8
Corn oil	1 tablespoon	1.9	-
Olive oil	1 tablespoon	1.9	0.1
Soybean oil	1 tablespoon	1.1	8.7
Sunflower seed kernels, dry roasted	1 ounce	7.4	0
Almonds	1 ounce	7.3	0.2
Hazelnuts	1 ounce	4.3	0
Peanuts	1 ounce	2.4	2.4
Pecans	1 ounce	0.4	6.9
Peanut butter, smooth	2 tablespoons	3.2	-
Tomato sauce, canned	1 cup	3.5	0.2
Cranberry juice	1 cup (8 fl oz)	3.0	-
Apricots, dried	½ cup (halves)	2.8	0
Avocado (California)	1 fruit	2.7	0.4
Fish, rainbow trout, cooked, dry-heat	3 ounces	2.4	0
Spinach, cooked, boiled	½ cup	1.9	-
Asparagus, canned	½ cup	1.5	-
Swiss chard, cooked, boiled	½ cup (chopped)	1.6	-
Broccoli, cooked, boiled	½ cup (chopped)	1.1	-
Blackberries, raw	½ cup	0.8	0.3

In the US, the average intake of α-tocopherol from food (including enriched and fortified sources) for adults (≥19 years of age) is 7.2 mg/day (25); this level is well below the RDA of 15 mg/day of α-tocopherol (see **Table 1**). While it appears feasible for individuals to meet the RDA from food only, Americans would have to depart from their current dietary practices and include greater intakes of nuts, seeds, fruit, and vegetables without increasing fat intake above recommended levels (96).

Supplements

RRR-α-tocopherol is the only stereoisomeric form of α-tocopherol found in unfortified foods. The same is not always true for nutritional supplements. Vitamin E supplements generally contain 100 IU to 1,000 IU of α-tocopherol. Supplements made from entirely natural sources contain only *RRR*-α-tocopherol (wrongly labeled *d*-α-tocopherol). *RRR*-α-tocopherol is the most bioavailable form of α-tocopherol in the body. Synthetic α-tocopherol, which is often found in fortified food and nutritional supplements and usually labeled *all-rac*-α-tocopherol or *dl*-α-tocopherol, include all eight possible stereoisomers of α-tocopherol (see Function). Because half of the isomers present as a mixture in synthetic α-tocopherol are not usable by the body, synthetic α-tocopherol is less bioavailable than natural α-tocopherol (see **Figure 1**). To calculate the amount (in milligrams) of α-tocopherol bioavailable in a supplement, the conversion factors are as follows:

- Natural vitamin E (*RRR*-α-tocopherol) containing supplements:
  IU of *RRR*-α-tocopherol x 0.67 = mg of *RRR*-α-tocopherol
  Example: 100 IU of natural vitamin E provides 67 mg of *RRR*-α-tocopherol
- Synthetic vitamin E (*all-rac*-α-tocopherol) containing supplements:
  IU of *all-rac*-α-tocopherol x 0.45 = mg of *RRR*-α-tocopherol
  Example: 100 IU of synthetic vitamin E provides 45 mg of 2*R*-α-tocopherol

In addition, vitamin E-fortified foods often contain synthetic α-tocopherol, and amounts of vitamin E are provided as a percentage of the daily value (DV) of 30 IU (approximately 20 mg of *RRR*-α-tocopherol).

α-Tocopheryl esters

α-Tocopheryl succinate and α-tocopheryl acetate are the main esterified forms of vitamin E in nutritional supplements. Tocopherol esters are more resistant to oxidation during storage than unesterified tocopherols (1). When taken orally, the succinate or acetate moieties are removed from α-tocopherol in the intestine. The bioavailability of α-tocopherol from α-tocopheryl succinate and α-tocopheryl acetate is equivalent to that of free α-tocopherol (97). Hence, the conversion factors used to determine the amount of bioavailable α-tocopherol provided by α-tocopheryl succinate and α-tocopheryl acetate are the same as those used for α-tocopherol (see above) (2). Cell culture studies indicated that the vitamin E ester, α-tocopheryl succinate, could inhibit proliferation and induce apoptosis in a number of cancer cell lines (12). Limited data from animal models of cancer found that α-tocopheryl succinate administered by injection inhibited tumor growth (98). There is currently no evidence in humans that taking oral α-tocopheryl succinate supplements delivers α-tocopheryl succinate to tissues. Of note, current research investigates nanomedicines to increase α-tocopheryl succinate bioavailability before exploring putative benefits in clinical settings (98).

α-Tocopheryl nicotinate is another α-tocopherol ester formed from synthetic α-tocopherol and nicotinic acid (niacin). While α-tocopheryl nicotinate can be prescribed as a lipid-lowering agent in Europe and Japan, it is marketed as a supplement only in the US (99).

α-Tocopheryl phosphates (Ester-E®)

There is currently no published evidence that supplements containing α-tocopheryl phosphates are more efficiently absorbed or have greater bioavailability in humans than those containing α-tocopherol (99).

Other supplemental forms

Supplements containing γ-tocopherol, mixed tocopherols, or tocotrienols are also commercially available (99). The amounts of α- and γ-tocopherol in mixed tocopherol supplements vary, so it is important to read the label to determine the amount of each tocopherol form present in a capsule.

Safety

Toxicity

Few side effects have been noted in adults taking supplements of less than 2,000 mg of α-tocopherol daily (either natural or synthetic vitamin E). However, most studies assessing safety issues or toxicity of α-tocopherol supplementation have lasted only a few weeks to a few months, and side effects associated with long-term α-tocopherol supplementation have not been adequately studied. The most worrisome possibility is that of impaired blood clotting, which increases the likelihood of hemorrhage in some individuals. A meta-analysis of randomized controlled trials found that daily vitamin E supplementation — equivalent to 25 to 536 mg/day of *RRR*-α-tocopherol — for several years resulted in a significant, 10% reduction in the risk of ischemic stroke (five trials, 91,393 participants) and a nonsignificant trend towards an increased risk of hemorrhagic stroke (five trials, 100,748 participants) (100).

A tolerable upper intake level (UL) for any form of supplemental α-tocopherol (all possible stereoisomers) has been established by the Food and Nutrition Board of the Institute of Medicine to avoid the potential risk of bleeding (**Table 3**). Specifically, the UL of 1,000 mg/day of α-tocopherol in any supplemental form (equivalent to 1,500 IU/day of *RRR*-α-tocopherol or 1,100 IU/day of *all-rac*-α-tocopherol) corresponds to the highest dose unlikely to result in hemorrhage in almost all adults (2). Although only certain isomers of α-tocopherol are retained in the circulation, all forms are absorbed and metabolized by the liver. Hence, the rationale for a UL that refers to all stereoisomers of α-tocopherol is based on the fact that any form of α-tocopherol (natural or synthetic) can be absorbed and thus be potentially harmful.

Table 3. Tolerable Upper Intake Level (UL) for α-Tocopherol*

Age Group	mg/day$^{\#}$
Infants 0-12 months	Not possible to establish$^{\#\#}$
Children 1-3 years	200
Children 4-8 years	300
Children 9-13 years	600
Adolescents 14-18 years	800
Adults 19 years and older	1,000

*The UL for α-tocopherol applies to all stereoisomers of α-tocopherol (natural and synthetic) found in supplements and fortified food.

$^{\#}$Of note, mg-to-IU conversion factors are such that the UL in IU for synthetic tocopherol (*all-rac*-α-tocopherol) is 1.10 times the UL in mg, and the UL in IU for natural tocopherol (*RRR*-α-tocopherol) is 1.50 times the UL in mg. Hence, the UL amount of 1,000 mg for adults corresponds to 1,100 IU of synthetic tocopherol or 1,500 IU of natural tocopherol.

$^{\#\#}$Source of intake should be from foods or formula only.

Some physicians recommend discontinuing high-dose vitamin E supplementation two to four weeks before elective surgery — including dental procedures — to decrease the risk of hemorrhage (99).

Because dietary vitamin E is essential to prevent vitamin E deficiency in the newborn, vitamin E must be supplied in parenteral nutrition solutions in infants who cannot be given enteral feeding, such as prematurely born infants. Yet, preterm infants appear to be especially vulnerable to adverse effects of α-tocopherol supplementation, and supplemental vitamin E should be administered only under controlled supervision by a pediatrician (101).

Finally, the results of only one randomized controlled trial in 601 patients with common forms of retinitis pigmentosa (RP) indicated that supplementation with 400 IU/day of synthetic vitamin E (equivalent to 180 mg/day of *RRR*-α-tocopherol) modestly but significantly accelerated the loss of retinal function compared to placebo (22). Patients with common forms of RP should therefore avoid taking high-dose vitamin E supplements if they are not deficient in vitamin E (see Deficiency).

Does vitamin E supplementation increase the risk of all-cause mortality?

A prospective observational study in over 4,000 participants of the Framingham Heart Study and the Framingham Offspring Study — with or without preexisting cardiovascular disease — found no statistically significant association between vitamin E supplement intake and cardiovascular or all-cause mortality after a 10-year follow-up period (102). However, in addition to reports of increased risk of hemorrhage and heart failure with supplemental vitamin E in several randomized controlled studies (see Cardiovascular disease), a meta-analysis by Miller et al. (103) suggested an increased risk of death with the use of large doses of vitamin E, yet lower than the UL. Specifically, this meta-analysis combined the results of 19 clinical trials of vitamin E supplementation that mostly focused on secondary prevention and, as such, included subjects with pre-existing conditions including heart disease, end-stage renal failure, and Alzheimer's disease. The study found that daily supplementation with at least 400 IU of synthetic vitamin E (equivalent to 180 mg of *RRR*-α-tocopherol) resulted in a 4% increase in risk of death from any cause compared to placebo (103). However, further dose-response analysis and adjustment for intake of other vitamin and mineral supplements indicated that all-cause mortality risk was significantly increased by 7% only at a dose of 2,000 IU/day, which is notably higher than the UL for adults (1,100 IU/day of synthetic tocopherol or 1,500 IU/day of natural tocopherol; see **Table 3**). Additionally, a more recent meta-analysis of 46 randomized trials, including 171,244 participants, found that supplemental vitamin E, singly or in combination with other antioxidants, did not significantly alter the risk of all-cause mortality (104). At present, there is no convincing evidence that vitamin E supplementation below the UL increases the risk of death from cardiovascular disease or other causes, especially in generally healthy subjects. Yet, individuals with pre-existing conditions may be at increased risk of serious adverse effects (including death) if one considers the possibility that large doses of supplemental vitamin E might interfere with medications, and possibly lower their efficacy or increase their toxicity (1).

Nutrient interactions

Large doses of vitamin E may inhibit vitamin K-dependent carboxylase activity and interfere with the coagulation cascade (see the article on Vitamin K) (19). Hence, the use of vitamin E supplements may increase the risk of bleeding in individuals taking anticoagulant drugs (blood thinners), such as heparin and the vitamin K antagonist, warfarin (Coumadin); antiplatelet drugs, such as clopidogrel (Plavix), ticlopidine (Ticlid), tirofiban (Aggrastat), and dipyridamole (Aggrenox); and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and others. In addition, individuals who may be vitamin K deficient due to liver failure, those with a propensity to bleed (e.g., bleeding peptic ulcers), and those with inherited bleeding disorders (e.g., hemophilia) or a history of hemorrhagic stroke, should not take α-tocopherol supplements without close medical supervision because of the increased risk of hemorrhage (20, 99). Finally, it cannot be excluded that vitamin E would potentiate the antithrombotic activity of supplemental fish oils and herbal products, such as garlic, curcumin, or Ginkgo biloba (99).

Drug interactions

A number of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, sucralfate, mineral oil, and the fat substitute, olestra, which interfere with fat absorption, may theoretically decrease the absorption of fat-soluble vitamins, including vitamin E. The anticonvulsant drugs phenobarbital, phenytoin (Dilantin), and carbamazepine (Tegretol), may also lower plasma vitamin E concentrations in individuals with epilepsy (105).

Antioxidants and statins (3-hydroxy-3-methylglutary-coenzyme A reductase inhibitors)

A three-year randomized controlled trial in 160 patients with coronary heart disease (CHD) and low high-density-lipoprotein (HDL) levels found that a combination of simvastatin (Zocor) and niacin increased the HDL2 subfraction level (considered the most cardioprotective), inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, such as myocardial infarction and stroke (106). Surprisingly, when an antioxidant combination of 1,000 mg of vitamin C, 800 IU (536 mg) of *RRR*-α-tocopherol, 100 μg of selenium, and 25 mg of β-carotene daily, was taken with the simvastatin-niacin combination, the protective effects were diminished. However, in a much larger randomized controlled trial of simvastatin and an antioxidant combination of 600 mg of *all-rac*-α-tocopherol (297 mg of *RRR*-α-tocopherol), 250 mg of vitamin C, and 20 mg of β-carotene daily in more than 20,000 men and women with CHD or diabetes, the antioxidant combination did not adversely affect the cardioprotective effects of simvastatin therapy over a five-year period (107). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplementation and cholesterol-lowering agents like statins.

Linus Pauling Institute Recommendation

The Recommended Dietary Allowance (RDA) for vitamin E for adult men and women is 15 mg (22.5 IU) per day. Notably, more than 90% of individuals two years of age and older in the US do not meet the daily requirement for vitamin E from food sources alone. Therefore, LPI recommends that generally healthy adults (aged 19 years and older) take a daily multivitamin/mineral (MVM) supplement, which usually contains 30 IU of synthetic vitamin E — equivalent to 13.5 mg of *RRR*-α-tocopherol and 90% of the RDA.

Older adults (>50 years)

The Linus Pauling Institute's recommendation to take a daily multivitamin/mineral (MVM) supplement containing vitamin E is also appropriate for generally healthy older adults. MVMs typically contain 30 IU of synthetic vitamin E, covering 90% of the RDA.

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Vitamin K

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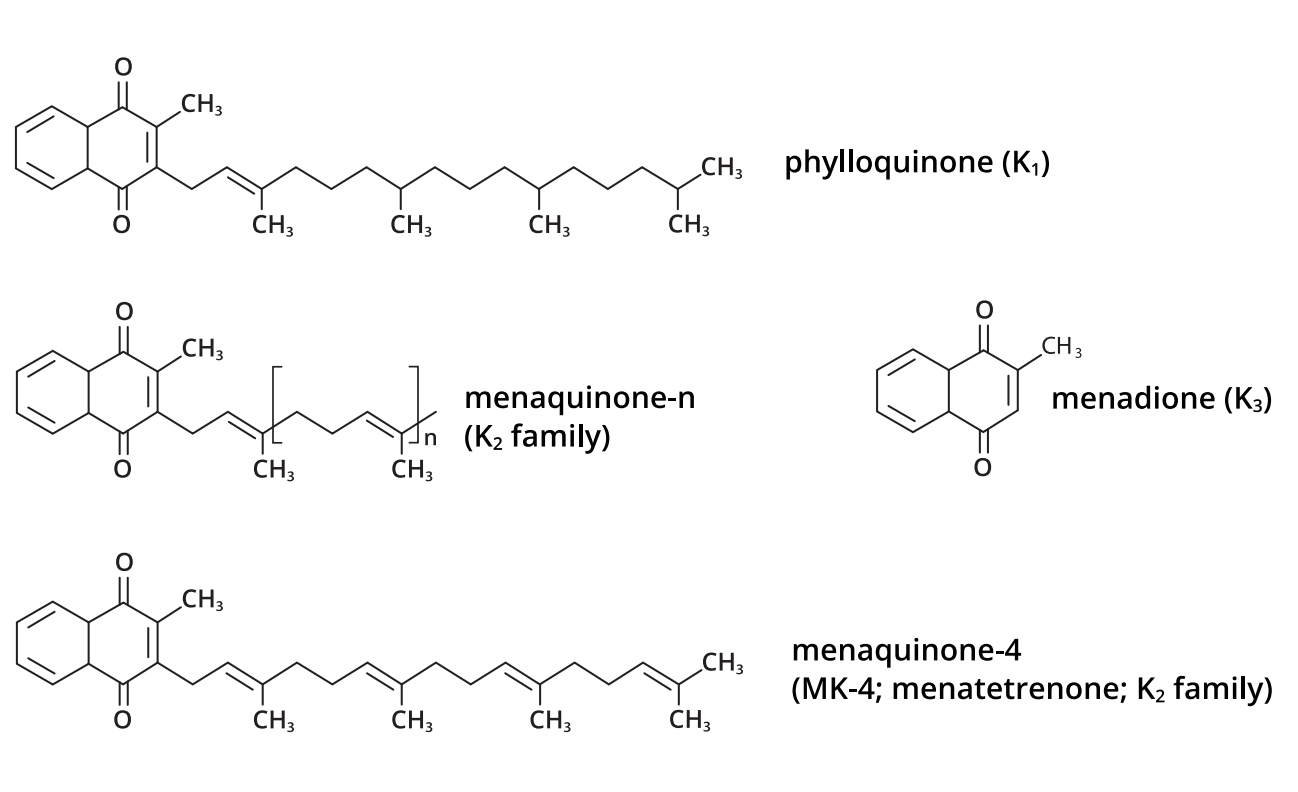
Summary

- Naturally occurring forms of vitamin K include phylloquinone (vitamin K_1) and a family of molecules called menaquinones (MKs or vitamin K_2). *(More information)*
- With limited vitamin K storage capacity, the body recycles vitamin K in the vitamin K oxidation-reduction cycle in order to reuse it multiple times. *(More information)*
- Vitamin K is the essential cofactor for the carboxylation of glutamic acid residues in many vitamin K-dependent proteins (VKDPs) that are involved in blood coagulation, bone metabolism, prevention of vessel mineralization, and regulation of various cellular functions. *(More information)*
- Vitamin K deficiency increases the risk of excessive bleeding (hemorrhage). An injection of vitamin K is recommended to protect all newborns from life-threatening bleeding within the skull. *(More information)*
- The adequate intake (AI) level for vitamin K is set at 90 μg/day for women and 120 μg/day for men. *(More information)*
- Vitamin K deficiency may impair the activity of VKDPs and increase the risk of osteoporosis and fractures. Some, but not all, observational studies have found lower vitamin K status to be associated with lower bone mineral density and higher fracture incidence. Overall, intervention trials have been inconclusive regarding the role of supplemental vitamin K (vitamin K_1 or vitamin K_2) in further reducing bone loss in otherwise calcium- and vitamin D-replete adults. *(More information)*
- Abnormal mineralization of blood vessels increases with age and is a major risk factor for cardiovascular disease. Vitamin K inadequacy may inactivate several VKDPs that inhibit the formation of calcium precipitates in vessels. There is only limited evidence of a benefit of supplemental vitamin K in the prevention of vessel calcification and cardiovascular events. *(More information)*
- While the results of a few observational studies suggest that low vitamin K status might have a role in development of osteoarthritis, randomized controlled trials are needed. *(More information)*
- Phylloquinone is found at high concentrations in green leafy vegetables and certain plant oils, while most menaquinones are usually found in cheese, animal products, and certain fermented foods. *(More information)*
- Several drugs, including vitamin K antagonists (e.g., warfarin), are known to interfere with vitamin K absorption and metabolism. *(More information)*

Vitamin K is a fat-soluble vitamin. Originally identified for its role in the process of blood clot formation ("K" is derived from the Danish word "koagulation"), vitamin K is essential for the functioning of several proteins involved in physiological processes that encompass, but are not limited to, the regulation of blood clotting (coagulation) (1). Naturally occurring forms of vitamin K include a number of vitamers known as vitamin K_1 and vitamin K_2 (**Figure 1**). Vitamin K_1 or phylloquinone is synthesized by plants and is the predominant form in the diet. Vitamin K_2 includes a range of vitamin K forms collectively referred to as menaquinones. Most menaquinones are synthesized by human intestinal microbiota and found in fermented foods and in animal products. Menaquinones differ in length from 1 to 13 repeats of 5-carbon units in the side chain of the molecules. These forms of vitamin K are designated menaquinone-n (MK-n), where n stands for the number of 5-carbon units (MK-2 to MK-13) (2, 3). Widely used in animal husbandry, the synthetic compound known as menadione (vitamin K_3) is a provitamin that needs to be converted to menaquinone-4 (MK-4) to be active (**Figure 1**) (4).

Figure 1. Chemical Structures of Vitamin K



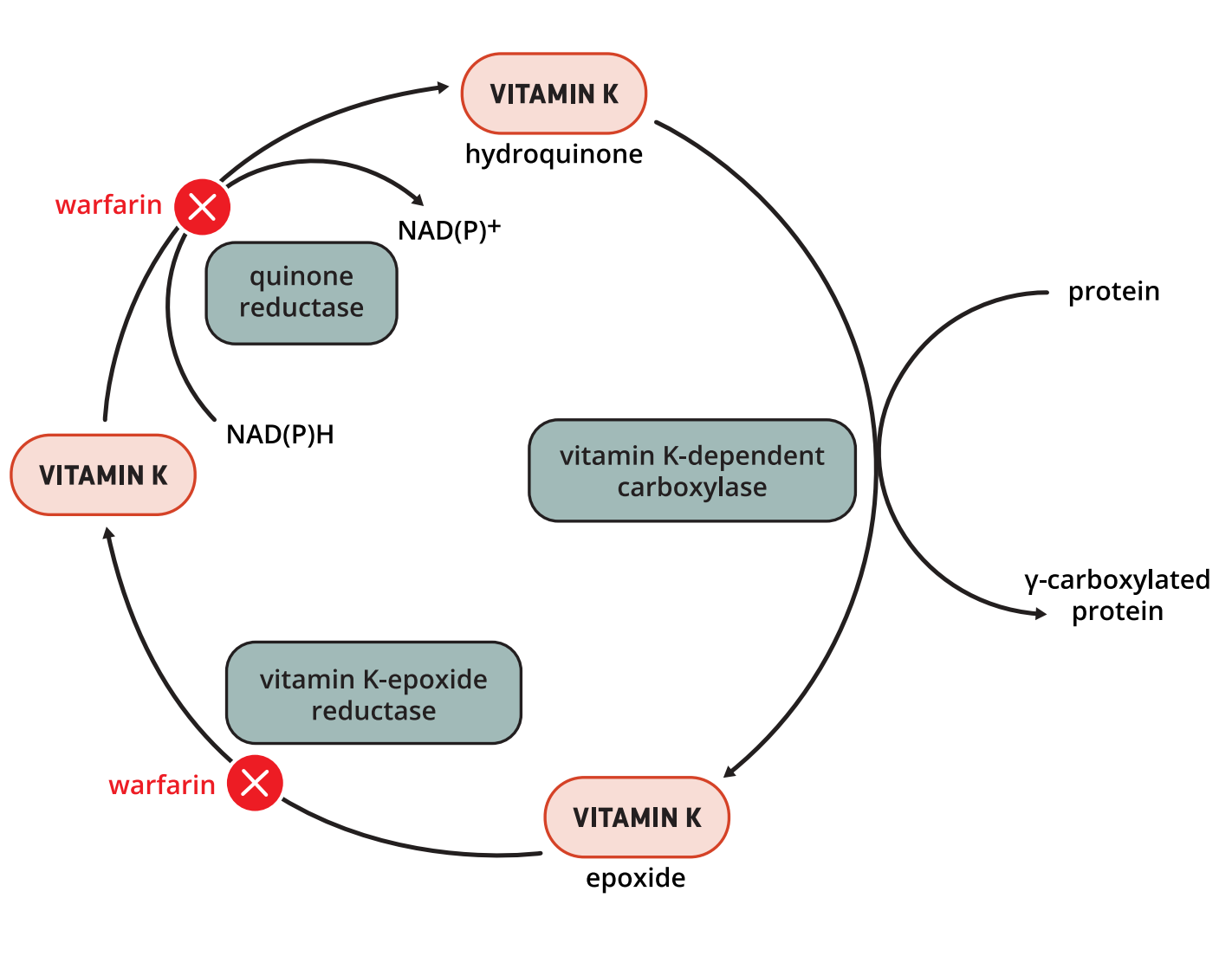
Function

Vitamin K functions as a cofactor for the enzyme, γ-glutamylcarboxylase, which catalyzes the carboxylation of the amino acid glutamic acid (Glu) to γ-carboxyglutamic acid (Gla). Vitamin K-dependent γ-carboxylation that occurs only on specific glutamic acid residues in identified vitamin K-dependent proteins (VKDP) is critical for their ability to bind calcium (5).

Vitamin K oxidation-reduction cycle

Although vitamin K is a fat-soluble vitamin, the body stores very small amounts that are rapidly depleted without regular dietary intake. Perhaps because of its limited ability to store vitamin K, the body recycles it through a process called the vitamin K-epoxide cycle (**Figure 2**). The vitamin K cycle allows a small amount of vitamin K to be reused many times for protein carboxylation, thus decreasing the dietary requirement. Briefly, vitamin K hydroquinone (reduced form) is oxidized to vitamin K epoxide (oxidized form). The reaction enables γ-glutamylcarboxylase to carboxylate selective glutamic acid residues on vitamin K-dependent proteins. The recycling of vitamin K epoxide (oxidized form) to hydroquinone (reduced form) is carried out by two reactions that reduce vitamin K epoxide (KO) to vitamin K quinone and then to vitamin K hydroquinone (KH_2; **Figure 2**). Additionally, the enzyme vitamin K-epoxide reductase (VKOR) catalyzes the reduction of KO to vitamin K quinone and may be involved — as well as another yet-to-defined reductase — in the production of KH2 from vitamin K quinone (6, 7). The anticoagulant drug warfarin acts as a vitamin K antagonist by inhibiting VKOR activity, hence preventing vitamin K recycling (see Coagulation).

Figure 2. The Vitamin K Cycle



The reduced form of vitamin K (hydroquinone) donates a pair of electrons to the vitamin K-dependent carboxylase (known as γ-glutamylcarboxylase), which carboxylates glutamic acid residues in specific vitamin K-dependent proteins. The resultant oxidized form of vitamin K (epoxide) is converted back to hydroquinone in a two-step reaction. The first step, which converts vitamin K epoxide to vitamin K, is catalyzed by vitamin K-epoxide reductase; the second step is catalyzed by either vitamin K-epoxide reductase or most likely by another yet-to-be-defined reductase. This pathway is inhibited by the vitamin K antagonist and anticoagulant drug, warfarin. The reduction of vitamin K to hydroquinone is also possibly catalyzed by a NAD(P)H-dependent reductase that is resistant to warfarin.

Coagulation

The ability to bind calcium ions (Ca^{2+}) is required for the activation of the several vitamin K-dependent clotting factors, or proteins, in the coagulation (clotting) cascade. The term 'coagulation cascade' refers to a series of events, each dependent on the other, that stops bleeding through clot formation. Vitamin K-dependent γ-carboxylation of specific glutamic acid residues in those proteins makes it possible for them to bind calcium. Factors II (prothrombin), VII, IX, and X make up the core of the coagulation cascade. Protein Z appears to enhance the action of thrombin (the activated form of prothrombin) by promoting its association with phospholipids in cell membranes. Protein C and protein S are anticoagulant proteins that provide control and balance in the coagulation cascade; protein Z also has an anticoagulatory function. Control mechanisms for the coagulation cascade exist since uncontrolled clotting may be as life threatening as uncontrolled bleeding. Vitamin K-dependent coagulation factors are synthesized in the liver. Consequently, severe liver disease results in lower blood levels of vitamin K-dependent clotting factors and an increased risk for uncontrolled bleeding (hemorrhage) (8).

Oral anticoagulant therapy with vitamin K antagonists

Some people are at increased risk of forming clots, which could block the flow of blood in arteries of the heart, brain, or lungs, resulting in myocardial infarction (heart attack), stroke, or pulmonary embolism, respectively. Abnormal clotting is not related to excessive vitamin K intake, and there is no known toxicity associated with vitamin K_1 or vitamin K_2 (see Toxicity). Some oral anticoagulants, such as warfarin (Jantoven, formerly known as Coumadin), inhibit coagulation by antagonizing the action of vitamin K. Warfarin prevents the recycling of vitamin K by blocking VKOR activity, thus creating a functional vitamin K deficiency (**Figure 2**). Inadequate γ-carboxylation of vitamin K-dependent coagulation proteins interferes with the coagulation cascade, which inhibits blood clot formation. Large quantities of dietary or supplemental vitamin K can overcome the anticoagulant effect of vitamin K antagonists; thus, patients taking these drugs are cautioned against consuming very large or highly variable quantities of vitamin K (see Drug interactions). Experts now advise a reasonably constant dietary intake of vitamin K that meets current dietary recommendations (90-120 μg/day) for patients taking vitamin K antagonists like warfarin (9, 10).

Skeletal formation and prevention of soft tissue calcification

Vitamin K-dependent γ-carboxylation is essential to several bone-related proteins, including osteocalcin, anticoagulation factor protein S, matrix γ-carboxylated glutamate (Gla) protein (MGP), Gla-rich protein (GRP), and periostin (originally called osteoblast-specific factor-2). Osteocalcin (also known as bone Gla protein) is synthesized by osteoblasts (bone-forming cells); the synthesis of osteocalcin is regulated by the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol). The calcium-binding capacity of osteocalcin requires vitamin K-dependent γ-carboxylation of three glutamic acid residues. Although its function in bone mineralization is not fully understood, osteocalcin is required for the growth and maturation of calcium hydroxyapatite crystals (see Osteoporosis) (11).

Protein S appears to play a role in the breakdown of bone mediated by osteoclasts. Individuals with inherited protein S deficiency suffer complications related to increased blood clotting, as well as osteonecrosis (12, 13). Protein S can bind and activate receptors of the TAM family that are involved in phagocytosis. Mutations in TAM receptors can result in visual impairment, defective spermatogenesis, autoimmune disorders, and platelet disorders (14).

MGP has been found in cartilage, bone, and soft tissue, including blood vessel walls, where it is synthesized and secreted by vascular smooth muscle cells. MGP is involved in the inhibition of calcification at various sites, including cartilage, vessel wall, skin elastic fibers, and the trabecular meshwork in the eye (see Vascular calcification) (15, 16). Moreover, several VKDPs, including MGP, have been associated with calcification sites in arteries, skin, kidneys, and eyes in certain inherited conditions, such as pseudoxanthoma elasticum and beta-thalassemia (17, 18).

The vitamin K-dependent proteins, GRP and periostin, are also synthesized in bone tissue, but their roles in bone metabolism are still unclear (19, 20). Expressed in normal human skin and vascular tissues, GRP has been colocalized with abnormal mineral deposits in the extracellular matrix in calcified arteries and calcified skin lesions (21). Expressed in most connective tissues, including skin and bone, periostin was initially associated with cell adhesion and migration. This VKDP also appears to promote angiogenesis (formation of new blood vessels) during cardiac valve degeneration and tumor growth (22, 23).

Current research suggests that reduced γ-glutamylcarboxylase activity and/or lower vitamin K bioavailability may impair the activity of VKDPs and contribute to bone mineralization defects and abnormal soft tissue calcification (see Disease Prevention) (24).

Regulation of cellular functions

Growth arrest-specific gene 6 protein (Gas6) is a vitamin K-dependent protein that was identified in 1993. It has been found throughout the nervous system, as well in the heart, lungs, stomach, kidneys, and cartilage. Identified as a ligand of the TAM family of transmembrane tyrosine kinase receptors, Gas6 appears to be a cellular growth regulation factor with cell-signaling activities. Gas6 has been involved in diverse cellular functions, including phagocytosis, cell adhesion, cell proliferation, and protection against apoptosis (5). It may also play important roles in the developing and aging nervous system (reviewed in 25). Further, Gas6 appears to regulate platelet signaling and vascular hemostasis (26). Expressed in most tissues and involved in many cellular functions, Gas6 has also been linked to several pathological conditions, including clot formation (thrombogenesis), atherosclerosis, chronic inflammation, and cancer growth (27-29).

Deficiency

Overt vitamin K deficiency results in impaired blood clotting, usually demonstrated by laboratory tests that measure clotting time. Symptoms include easy bruising and bleeding that may be manifested as nosebleeds, bleeding gums, blood in the urine, blood in the stool, tarry black stools, or extremely heavy menstrual bleeding. In infants, vitamin K deficiency may result in life-threatening bleeding within the skull (intracranial hemorrhage) (8).

Multiple biomarkers of vitamin K status exist (reviewed in 30), but only impaired blood coagulation is used as a measure of clinical vitamin K deficiency.

Adults

Vitamin K deficiency is uncommon in healthy adults for a number of reasons: (1) vitamin K is widespread in foods (see Food sources); (2) the vitamin K cycle conserves vitamin K (see Vitamin K oxidation-reduction cycle); and (3) bacteria that normally inhabit the large intestine synthesize menaquinones (vitamin K_2), although it is unclear whether significant amounts are absorbed and utilized (see Food sources). Adults at risk for vitamin K deficiency include those taking vitamin K antagonists and individuals with significant liver damage or disease (8). Additionally, individuals with fat malabsorption disorders, including inflammatory bowel disease and cystic fibrosis, may be at increased risk of vitamin K deficiency (31-34).

Infants

Newborn babies who are exclusively breast-fed are at increased risk for vitamin K deficiency because human milk is relatively low in vitamin K compared to formula. Newborn infants, in general, have low vitamin K status for the following reasons: (1) vitamin K transport across the placental barrier is limited; (2) liver storage of vitamin K is very low; (3) the vitamin K cycle may not be fully functional in newborns, especially premature infants; (4) the vitamin K content of breast milk is low, and immature gut flora (5, 35). Infants whose mothers are on anticonvulsant medication to prevent seizures are also at risk for vitamin K deficiency. Vitamin K deficiency in newborns may result in a bleeding disorder called vitamin K deficiency bleeding (VKDB) of the newborn (reviewed in 36). Because VKDB is life threatening and easily prevented, the American Academy of Pediatrics and a number of similar international organizations recommend that an intramuscular dose of phylloquinone (vitamin K_1) be administered to all newborns shortly after birth (reviewed in 37).

Controversies around vitamin K administration to newborns

Vitamin K and childhood leukemia: In the early 1990s, two retrospective studies were published suggesting a possible association between phylloquinone injections in newborns and the development of childhood leukemia and other forms of childhood cancer. However, two large retrospective studies in the US and Sweden, which reviewed the medical records of 54,000 and 1.3 million children, respectively, found no evidence of a relationship between childhood cancers and phylloquinone injections at birth (38, 39). Moreover, a pooled analysis of six case-control studies, including 2,431 children diagnosed with childhood cancer and 6,338 cancer-free children, found no evidence that phylloquinone injections for newborns increased the risk of childhood leukemia (40). In a policy statement, the American Academy of Pediatrics recommended that routine vitamin K prophylaxis for newborns be continued because VKDB is life threatening and the risks of cancer are unproven and unlikely (41). In the last decade, physicians have reported a rise in late-onset cases of VKDB due to an increasing trend of parental omission or refusal of newborn vitamin K prophylaxis (42, 43).

Lower doses of vitamin K_1 for premature infants: The results of two studies of vitamin K levels in premature infants suggest that the standard initial dose of phylloquinone (vitamin K_1) for full-term infants (1.0 mg) may be too high for premature infants (44, 45). These findings have led some experts to suggest the use of an initial phylloquinone dose of 0.3 mg/kg for infants with birth weights of less than 1,000 g (2 lbs, 3 oz), and an initial phylloquinone dose of 0.5 mg would probably prevent hemorrhagic disease in newborns (44). Yet, additional studies are needed to determine the best vitamin K prophylaxis in premature infants (46).

The Adequate Intake (AI)

In 2001, the US Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) established the adequate intake (AI) level for vitamin K based on phylloquinone intake levels in healthy individuals (**Table 1**). The AI for infants was based on estimated intake of vitamin K from breast milk (47). The FNB did not consider menaquinone intakes; data on menaquinone consumption are limited (48).

Table 1. Adequate Intake (AI) for Vitamin K

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	2.0	2.0
Infants	7-12 months	2.5	2.5
Children	1-3 years	30	30
Children	4-8 years	55	55
Children	9-13 years	60	60
Adolescents	14-18 years	75	75
Adults	19 years and older	120	90
Pregnancy	18 years and younger	-	75
Pregnancy	19 years and older	-	90
Breast-feeding	18 years and younger	-	75
Breast-feeding	19 years and older	-	90

Disease Prevention

Osteoporosis

The discovery of vitamin K-dependent proteins in bone has led to research on the role of vitamin K in maintaining bone health.

Vitamin K and bone health: observational studies

Vitamin K_1: Observational studies have found a relationship between phylloquinone (vitamin K_1) and age-related bone loss (osteoporosis). The Nurses' Health Study followed more than 72,000 women for 10 years. In an analysis of this cohort, women whose phylloquinone intakes were lower than 109 micrograms/day (μg/day) had a 30% higher risk for hip fracture compared to women with intakes equal to or above 109 μg/day (49). Another prospective study in over 800 elderly men and women, followed in the Framingham Heart Study for seven years, found that participants with dietary vitamin K intakes in the highest quartile (median, 254 μg/day) had a 65% lower risk of hip fracture than those with intakes in the lowest quartile (median, 56 μg/day) (50). Osteoporotic fractures are often linked to a reduction in bone mineralization. Yet, the investigators found no association between dietary phylloquinone intake and bone mineral density (BMD) in the Framingham subjects (50). While other studies failed to observe associations between dietary phylloquinone intake and measures of bone strength, BMD, or fracture incidence (51, 52), the cross-sectional study of a cohort of 3,199 middle-aged women found that subjects in the highest quartile of dietary phylloquinone intake had significantly greater hip and lumbar spine BMD than those in the lowest quartile (162 μg/day vs. 59 μg/day) (53). Moreover, cross-sectional and case-control studies have reported associations between higher phylloquinone intakes and lower incidence of hip fracture (54, 55).

However, because green leafy vegetables are the primary dietary source of phylloquinone and because they are usually part of a balanced diet, high phylloquinone consumption may simply be an indicator of healthy eating habits, which may — rather than phylloquinone itself — account for all or part of the association reported in observational studies (56).

The few studies that measured plasma phylloquinone generally found that higher circulating levels were associated with lower fracture risk (15, 57, 58). For example, the incidence of vertebral fractures was inversely correlated with lumbar BMD and plasma phylloquinone in a four-year prospective study that included 379 Japanese women ages 30-88 years (57). Yet, observational studies are not designed to making causal inferences, and only randomized controlled trials can evaluate whether phylloquinone may have beneficial effects on bone health (see Vitamin K supplementation studies and osteoporosis).

Vitamin K_2: There are few studies on associations between menaquinones (vitamin K_2) and bone health, perhaps because of the limited number of dietary sources of menaquinone-4 (MK-4), the main form of vitamin K_2 present in Western diets. The Japanese food natto, made of cooked soybeans fermented by *Bacillus subtilis natto*, is rich in MK-7. In a prospective cohort study that followed 944 Japanese women (ages 20-79 years), total hip BMD at baseline was positively associated with natto intake in postmenopausal women (59). During the three-year follow-up period, the rate of BMD loss at the femoral neck was significantly lower in women consuming natto (>200 μg/day of MK-7) compared to non-consumers. No association was found between natto intake and BMD in premenopausal women (59).

Total hip and femoral neck BMD was also reportedly higher in nearly 2,000 Japanese men aged 65 years and older who regularly consumed at least of one pack per day of natto (≥350 μg/day of MK-7) compared to those consuming less than one pack per week (<50 μg/day of MK-7) (60). Yet, increasing natto consumption also maximizes the intake of other dietary compounds (e.g., soy isoflavones) that have potential benefits for skeletal health; thus, there is need to find reliable measures of vitamin K status. To date, observational studies have failed to unequivocally support an association between circulating menaquinone (MK-7 and MK-4) levels and fracture risk (15, 61).

A meta-analysis that pooled the results of four prospective cohort studies and one nested case-control study found higher total dietary vitamin K intakes to be associated with a lower risk of total fracture (RR, 0.78; 95% CI: 0.56, 0.99) (62). In a recent Japanese cohort study not included in this meta-analysis (i.e., the Murakami Cohort Study), a protective association of dietary vitamin K intake was seen for vertebral fractures (p=0.005); vitamin K intake was not associated with total fracture in women or with either vertebral or total fracture in men (63).

Biomarker of vitamin K status and bone health

Total circulating levels of the bone protein, osteocalcin (OC), have been shown to be sensitive markers of bone formation. Several hormones and growth factors, including vitamin D but not vitamin K, regulate osteocalcin synthesis by osteoblasts. However, vitamin K is an essential cofactor for the γ-carboxylation of three glutamic acid residues in osteocalcin. Undercarboxylation of osteocalcin in human bone and serum has been linked to poor vitamin K status. The degree of osteocalcin γ-carboxylation is responsive to vitamin K nutritional interventions, and thus is used as a relative indicator of vitamin K status (11).

Circulating levels of uncarboxylated osteocalcin (ucOC) were found to be higher in postmenopausal women than premenopausal women and markedly higher in women over the age of 70. Also, high ratios of ucOC to total OC (ucOC/OC) appear to be predictive of hip fracture risk in elderly women (64, 65). Although vitamin K deficiency would seem the most likely cause of elevated blood ucOC/OC ratio, some investigators have documented an inverse relationship between biochemical measures of vitamin D nutritional status and ucOC levels, as well as a significant lowering of ucOC/OC ratio by vitamin D supplementation (66). It has been suggested that increased circulating ucOC/OC ratio could reflect a poor overall nutritional status that would include vitamin D inadequacy, which would explain the above-mentioned observations (67). However, in several randomized, placebo-controlled intervention studies conducted in young girls (67, 68) and postmenopausal women (69), vitamin D supplementation failed to decrease ucOC/OC ratios or show any additive effect on ucOC/OC lowering by supplemental vitamin K.

Vitamin K supplementation studies and osteoporosis

Vitamin K_1 supplementation: The review of five randomized clinical trials that assessed the effect of phylloquinone (vitamin K_1) supplementation on hip BMD using doses ranging from 200 μg/day to 5,000 μg/day for durations of 12 to 36 months found little promising benefit for bone health (15). Although supplementation with phylloquinone decreased ucOC levels in all five studies, only one study reported an effect of supplemental phylloquinone on BMD (70). In this study, 150 postmenopausal women were randomized to receive a placebo, minerals (500 mg/day of calcium, 150 mg/day of magnesium, and 10 mg/day of zinc) plus vitamin D (320 IU/day), or minerals, vitamin D, and phylloquinone (1,000 μg/day). The rate of BMD loss at the femoral neck, but not at the lumbar spine, was significantly lower in subjects with supplemental phylloquinone compared to the other two groups. Thus, evidence of a putative benefit of phylloquinone on bone health in older adults is considered weak. None of the studies were designed to assess the effect of phylloquinone on osteoporotic-related fractures. Further investigation may seek to evaluate whether phylloquinone supplementation could improve skeletal health in subjects at high-risk for vitamin K inadequacy (e.g., individuals with malabsorption syndromes or cystic fibrosis).

Vitamin K_2 supplementation: Pharmacological doses of menaquinone-4 (MK-4; brand name, menatetrenone) are currently used in Japan in the treatment of osteoporosis (71). Accordingly, most intervention trials investigating the effect of high-dose MK-4 on bone loss have been conducted in Japanese postmenopausal women. In a three-year placebo-controlled trial among postmenopausal women with osteopenia, adding a MK-7 supplement (375 μg/day) to combined calcium-vitamin D supplementation did not affect BMD or other bone health parameters despite reductions in serum ucOC (72). At present, the potential role for supplemental menaquinones on bone health still needs to be established in large, randomized, and well-controlled trials.

A 2019 systematic review and meta-analysis of clinical trials in postmenopausal women or women with osteoporosis found vitamin K supplementation — of any form — lowered risk of clinical fracture compared to controls (OR, 0.72; 95% CI, 0.55-0.95; 9 trials varying from 6 months to 2 years: 3 using phylloquinone, 5 using MK-4, and 1 using MK-7) (73). However, no benefit of vitamin K supplementation was seen for vertebral fractures (7 trials) or BMD (22 trials). The authors of this meta-analysis noted that the high heterogeneity of the included trials (i.e., form and dose of vitamin K, use of other supplements and drugs by participants, and treatment length) makes it difficult to inform clinical recommendations (73).

Vitamin K antagonists and bone health

Certain oral anticoagulants, such as warfarin, are known to be antagonists of vitamin K (see Coagulation). Few studies have examined chronic use of warfarin and risk of fracture in older women. One study reported no association between long-term warfarin treatment and fracture risk (74), while another one found a significantly higher risk of rib and vertebral fractures in warfarin users compared to nonusers (75). Additionally, a study in elderly patients with atrial fibrillation reported that long-term warfarin treatment was associated with a significantly higher risk of osteoporotic fracture in men but not in women (76). A meta-analysis of the results of 11 published studies found that oral anticoagulation therapy was associated with a very modest reduction in BMD at the wrist and no change in BMD at the hip or spine (77). The development of new anticoagulants that do not block vitamin K recycling may offer a safer alternative to the use of vitamin K antagonists (78).

Cardiovascular disease

Observational studies examining vitamin K intake in relation to cardiovascular-related mortality have found conflicting results (48). An inverse relationship between vitamin K intake and mortality was reported in a US national survey (NHANES III) of 3,401 participants (79). Adequate vs. inadequate vitamin K intakes (based on sex-specific AI: 90 μg/day for women and 120 μg/day for men) were associated with a 22% lower risk of cardiovascular disease (CVD)-related mortality and a 15% lower risk of all-cause mortality. The report also indicated that, while over two-thirds of individuals with chronic kidney disease had vitamin K intakes below the AI, the risk of CVD mortality was 41% lower in those with adequate compared to suboptimal intakes (79). However, higher vitamin K intakes were not associated with lower CVD mortality in a prospective study that followed 7,216 older adults at risk for developing CVD (80). This study associated higher intakes of phylloquinone, but not of menaquinones, with lower risk of all-cause mortality. More recently, in a prospective study that followed a cohort of 33,289 Dutch men and women for an average of 16.8 years (the EPIC-Netherlands), neither phylloquinone intake nor menaquinone intake at baseline was associated with mortality from cardiovascular disease, coronary heart disease, stroke, or all causes (81). Yet, a prospective study of 56,048 men and women participating in the Danish Diet, Cancer, and Health cohort reported higher phylloquinone intakes to be associated with lower risks of both cardiovascular disease-related mortality and all-cause mortality (82). Moreover, a few studies have examined the association of fasting circulating phylloquinone with cardiovascular-related or all-cause mortality. In a recent meta-analysis of individual participant data from three prospective cohort studies (the Multi-Ethnic Study of Atherosclerosis; the Health, Aging, and Body Composition Study, and the Framingham Offspring Study), a blood phylloquinone concentration less than or equal to 0.5 nmol/L (n=1,081) was associated with a 19% higher risk of all-cause mortality compared to a blood concentration >1.0 nmol/L (n=1,698; 83). This analysis did not find circulating phylloquinone to be linked with incident cardiovascular disease (83).

Observational studies offer limited support of an inverse relationship between phylloquinone intake and risk of incident cardiovascular disease, despite high intakes being sometimes regarded as a marker of healthy dietary habits associated with low cardiovascular risk (reviewed in 84). A prospective cohort study of 16,057 Dutch women (ages 49-70 years), followed for a mean period of 8.1 years, found a 9% reduction in risk for coronary heart disease (CHD) per each incremental 10 μg/day increase in menaquinone intake (85). In another earlier Dutch study that examined 4,807 healthy men and women 55 years and older, participants in the highest tertile of menaquinone intake (>32.7 μg/day) had a 41% lower risk of incident CHD and a 26% lower risk of all-cause mortality than those in the lowest tertile (<21.6 μg/day) (86). In addition, menaquinone intake was found to be inversely associated with aortic calcification, a major risk factor for CVD (86). A smaller prospective study among 2,987 Norwegian adults, followed for an average of 10.8 years, reported higher dietary intakes of vitamin K_2, but not of vitamin K_1, were associated with a lower risk of CHD (87). While these data are interesting, it is important to note that vitamin K_2 may solely be a marker of a heart-healthy diet and might not itself be cardioprotective. Most recently, the prospective Danish Diet, Cancer, and Health Study followed 53,372 older adults for an average of 21 years, finding both phylloquinone and menaquinone intake at baseline to be inversely associated with hospitalizations due to atherosclerotic cardiovascular events, including ischemic heart disease, ischemic stroke, and peripheral arterial disease (88).

Large-scale supplementation trials are needed to determine whether vitamin K_1 or vitamin K_2 reduces the risk of CHD or cardiovascular-related events like myocardial infarction or stroke.

Vascular calcification

One of the hallmarks of cardiovascular disease is the presence of atherosclerotic plaques in arterial walls. Plaque rupture that causes blood clot formation (thrombogenesis) is the usual cause of a myocardial infarction (heart attack) or stroke. While calcification of the plaques occurs as the atherosclerosis progresses, it is unclear whether calcification increases plaque instability and could predict risk of rupture and thrombogenesis (89). However, calcification may be predictive of future cardiovascular events, especially in those with chronic kidney disease (90). A meta-analysis of 30 prospective cohort studies, including a total of 218,080 participants, found that the presence of vascular calcification was associated with an overall three- to four-fold increased risk of cardiovascular events and mortality (91). An early population-based study of postmenopausal women (ages, 60-79 years) observed that the younger women (60-69 years) with aortic calcifications had lower vitamin K intakes than those without aortic calcifications, but this was not true for older women (70-79 years) (92). A prospective cohort study in 807 men and women, 39-45 years of age, did not find any correlation between dietary phylloquinone intake and coronary artery calcification, as measured non-invasively by computed tomography (93). Additionally, neither phylloquinone nor menaquinone intake was associated with calcification of breast arteries in a cross-sectional study of 1,689 women ages 49-70 years (94). However, in another cross-sectional study, the upper *vs*. lowest quartile of menaquinone (MK-4 to MK-10) intake (median intakes, 48.5 μg/day vs. 18 μg/day) was found to be associated with a 20% reduced prevalence of coronary artery calcification in 564 postmenopausal women (95).

Research has uncovered possible mechanisms by which vitamin K may inhibit mineralization (calcification) of vessels while promoting bone mineralization. The potential mechanisms, although not yet fully understood, implicate vitamin K-dependent proteins, including matrix Gla protein (MGP), Gla-rich protein (GRP), and Gas6 (96-98). Secreted by various cell types, such as vascular smooth muscle cells (VSMCs) in arterial vessel walls, MGP appears to be important for the prevention of calcification of soft tissues, including cartilage, vasculature, skin, and trabecular meshwork cells in the eye (15, 99). In MGP knockout mice, conversion of VSMCs into bone-like cells and extensive vessel calcification results in large vessel rupture and premature death. In humans, defective *MGP* gene has been linked to Keutel syndrome, a rare inherited condition characterized in particular by abnormal cartilage calcification and pulmonary artery stenosis (narrowing). Calcification prevention by MGP involved several mechanisms, including the binding to calcium crystals and the inhibition of proteins (bone morphogenic proteins; BMPs) known to promote ectopic bone formation (reviewed in 100).

Calcium-binding activity of MGP is regulated by two types of modifications (known as post-translational modifications since they take place after protein synthesis): the vitamin K-dependent carboxylation of up to five Glu residues and the phosphorylation of serine residues. A variation in the sequence (polymorphism) of the gene for MGP leading to a threonine-to-alanine transition in one of the five Gla domains of the protein may possibly prevent carboxylation and elicit a change in MGP ability to bind calcium. This polymorphism, known as *MGP*Thr83Ala, has been associated with the progression of coronary artery calcification over a mean period of 10.6 years in a community-based prospective study that followed 605 middle-aged men and women (101). This association was only observed among participants without detectable calcification at baseline and not in those who had baseline calcification (101). Interestingly, *MGP*Thr83Ala was also associated with higher risk of myocardial infarction and femoral artery calcification in carriers of the genotype (102).

Additionally, a small study initially found that, while undercarboxylated MGP (ucMGP) was absent from the innermost lining of the carotid arteries in healthy subjects, the majority of MGP in the carotid arterial lining of patients with atherosclerosis was undercarboxylated (103). In another study that examined the association between circulating MGP and incident cardiovascular events in 577 older men and women followed for a mean period of 5.6 years, the risk of cardiovascular disease (i.e., coronary artery disease, peripheral arterial disease, and cerebrovascular disease) was two- to three-fold greater in subjects in the highest *vs*. lowest tertile of plasma dephosphorylated and undercarboxylated MGP (dp-ucMGP) (104). The results of another prospective study suggested that circulating dp-ucMGP may be predictive of mortality risk in subjects with overt vascular disease (105). Indeed, the risk of cardiovascular-related and all-cause mortality was found to be nearly doubled in subjects with coronary artery disease or stroke in the highest *vs*. lowest quartile of dp-ucMGP concentrations (105).

Because suboptimal vitamin K nutritional status may limit carboxylation and result in biologically inactive ucMGP, it has been speculated that vitamin K supplementation may protect against vascular calcification. A three-year, double-blind, controlled trial investigated the potential effect of vitamin K on the progression of coronary calcification in 401 older, community-dwelling adults (ages, 60-80 years) free of cardiovascular disease at baseline (106). The participants were randomized to receive a daily multivitamin plus calcium and vitamin D with or without 500 mg of phylloquinone. Using measurements of coronary artery calcification at baseline and follow up, it was found that phylloquinone supplementation was able to limit the progression of vascular calcification and reduce plasma dp-ucMGP compared to control (106, 107). Although circulating dp-ucMGP was correlated to various markers of vitamin K status, no association with measures of coronary artery calcification were found (107). Smaller trials in those at high risk for coronary artery disease (108) or with existing aortic valve calcification (109), type 2 diabetes mellitus (110), or kidney disease (111, 112) have reported no benefit of vitamin K_2 supplementation on progression of vascular calcification. A meta-analysis of controlled clinical trials found that vitamin K supplementation reduced dp-ucMGP (7 trials), reduced ucOC (4 trials), and decreased progression of vascular calcification (3 trials) (113). Yet, the authors emphasize that any conclusions from their pooled analysis are limited by the high heterogeneity of the trials with respect to the form and dose of vitamin K utilized, as well as the assays that assessed vascular calcification (113).

Thus, further investigations are necessary to examine the role of other vitamin K-dependent proteins (e.g., GRP, periostin, Gas6) in human atherosclerotic plaque calcification and to evaluate the effect of supplemental vitamin K on the progression of vascular calcification and risk of cardiovascular disease.

Vitamin K antagonists and vascular calcification

Several cross-sectional studies have reported increased vascular calcium scores (a means to quantify vascular calcification) in chronic users of vitamin K antagonists compared to nonusers (reviewed in 114). Warfarin therapy has also been associated with higher circulating concentrations of dp-ucMGP in a prospective study that examined vascular calcification in subjects with cardiovascular disease (105). Newly developed direct inhibitors of coagulation factors that do not interfere with VKDP activity may be more suitable than vitamin K antagonists, especially with regards to vascular calcification (114).

Osteoarthritis

Osteoarthritis, a degenerative joint condition that affects more than 32 million US adults (115), is characterized by the breakdown of articular cartilage (i.e., cartilage within the joint). Because several vitamin K-dependent proteins are present in cartilage and in bone (116), vitamin K inadequacy may have a role in the development of osteoarthritis. A few observational studies have investigated a possible link between vitamin K intake or status and osteoarthritis. A cross-sectional study among 719 Japanese older adults found dietary intake of vitamin K to be inversely associated with knee osteoarthritis (117). In the Framingham Offspring Study (n=672; mean age, 66 years), higher plasma concentrations of phylloquinone were associated with a lower risk of hand, but not knee, osteoarthritis (118). A longitudinal study of 1,180 US adults (mean age, 62 years) found that low plasma concentrations of phylloquinone (≤0.5 nM) at baseline — indicative of a subclinical vitamin K deficiency — were associated with a 56% increase in risk of knee osteoarthritis after 30 months compared to those with higher plasma concentrations (119). In a more recent longitudinal study among 523 older US adults participating in the Health, Aging, and Body Composition Study, those with extremely low plasma concentrations of phylloquinone (<0.2 nM) at baseline had increased progression of knee osteoarthritis over three years, assessed by MRI of articular cartilage and the meniscus; those with higher plasma concentrations experienced no significant progression of knee osteoarthritis (120). Moreover, recent studies have associated use of the vitamin K antagonist drugs with higher risks of osteoarthritis (121) and joint replacement (121) of the knee and hip compared to nonusers.

While these observational data are interesting, randomized controlled trials are needed to determine whether vitamin K supplementation in those with low vitamin K status might help prevent or treat osteoarthritis. In an ancillary study of a double-blind, controlled trial examining the effects of vitamin K supplementation on bone loss and vascular calcification in older adults, no effects of phylloquinone supplementation (500 μg/day) were found on incidence of hand osteoarthritis after three years (122). Study participants were not screened for vitamin K status, and in a subgroup analysis, those with serum phylloquinone ≤1 nM at baseline that reached >1 nM at year 3 had less joint deterioration. These data infer that only those individuals with low vitamin K status benefit from vitamin K supplementation. Unfortunately, no measures were available for knee osteoarthritis, and it is well established that hand and knee osteoarthritis represent different phenotypes. Additional clinical trials that specifically examine the effect of vitamin K supplementation on osteoarthritis development are needed, especially in those with inadequate vitamin K status.

Sources

A US national survey, NHANES 2011-2012, found that average dietary intakes of vitamin K (all forms) vary greatly among individuals, with values ranging from 80 to 195 μg/day of phylloquinone for men and 78 to 223 μg/day of phylloquinone for women (123). Mean intakes for both men and women were 117 μg/day of phylloquinone; however, 57% of men and 37% of women did not meet the Adequate Intake (AI) level (123).

Food sources

Vitamin K_1

Phylloquinone (vitamin K_1) is the major dietary form of vitamin K in most diets. Green leafy vegetables and some plant oils (soybean, canola, olive, and cottonseed) are major contributors of dietary vitamin K. Mixed dishes have also been found to significantly contribute to vitamin K intake in the US (123). However, phylloquinone bioavailability from green vegetables is lower than from oil or supplements. Also, the phylloquinone content of green vegetables depends on their content in chlorophyll (green pigment), so that outer leaves have more phylloquinone than inner leaves. The efficiency of phylloquinone intestinal absorption varies among plant sources and is increased with the addition of a fat source to a meal. Finally, the hydrogenation of vegetable oils may decrease the absorption and biological effect of dietary phylloquinone (reviewed in 2, 9). If you wish to check foods for their nutrient content, including phylloquinone, search USDA's FoodData Central. A number of phylloquinone-rich foods are listed in **Table 2**, with their content in phylloquinone expressed in micrograms (μg).

Table 2. Some Food Sources of Phylloquinone

Food	Serving	Phylloquinone (μg)
Kale, frozen, boiled	1 cup	493
Chard, raw	1 cup	299
Parsley, raw	¼ cup	246
Broccoli, cooked	1 cup	220
Spinach, raw	1 cup	121
Watercress, raw	1 cup	85
Cabbage, green, raw	1 cup	68
Romaine lettuce, raw	1 cup	44
Soybean oil	1 Tablespoon	26
Canola oil	1 Tablespoon	10
Olive oil	1 Tablespoon	8
Cottonseed oil	1 Tablespoon	3

Vitamin K_2

Menaquinones (vitamin K_2) are primarily of microbial origins and thus commonly found in fermented foods, such as cheese, curds, and natto (fermented soybeans) (124, 125). MK-4 is the only menaquinone that is not produced by bacteria. MK-4 is formed from menadione (a synthetic form of vitamin K) found in animal feeds or is converted in a tissue-specific way from multiple dietary forms of vitamin K, including phylloquinone and various menaquinones (4, 126). Menaquinone-4 is found in dairy products, including milk, and in some meats (125). Longer chain menaquinones are found in limited fermented food products. The Japanese fermented soybean-based, natto, is rich in MK-7 (998 μg/100 g) and also contains MK-8 (84 μg/100 g). Some cheeses contain MK-8 and MK-9 (2, 125). Additionally, animal livers are a source of long-chain menaquinones (MK-7 to MK-13) (9).

Food composition databases, including USDA's FoodData Central, have limited data on menaquinone content in foods. Thus, menaquinone contribution to total vitamin K intakes is difficult to estimate and likely to vary between populations with different food consumption practices (2, 125). Bacteria that normally colonize the large intestine (colon) can synthesize menaquinones. It was initially thought that up to 50% of the human vitamin K requirement might be met by bacterial synthesis. However, all forms of vitamin K are absorbed in the small intestine via a mechanism requiring bile salts, while most of the menaquinone production takes place in the colon where bile salts are lacking. Current research suggests that the contribution of bacterial synthesis to vitamin K status is much less than previously thought, although the exact contribution remains unclear (16, 127).

Supplements

In the US, both phylloquinone and menaquinones are available without a prescription in multivitamin, single-nutrient, or multiple-nutrient supplements in varying doses; vitamin K content of multivitamins typically range from 20 to 120 μg per tablet (128). The US Food and Drug Administration (FDA) has not authorized any health claims for any forms of vitamin K.

Safety

Toxicity

Although allergic reactions are possible, there is no known toxicity associated with high doses (dietary or supplemental) of the phylloquinone (vitamin K_1) or menaquinone (vitamin K_2) forms of vitamin K (47). The same is not true for synthetic menadione (vitamin K_3) and its derivatives. Menadione can interfere with the function of glutathione, one of the body's natural antioxidants, resulting in oxidative damage to cell membranes. Menadione given by injection has induced liver toxicity, jaundice, and hemolytic anemia (due to the rupture of red blood cells) in infants; therefore, menadione is no longer used for treatment of vitamin K deficiency (5). No tolerable upper intake level (UL) has been established for vitamin K (47).

Nutrient interactions

Large doses of vitamin A and vitamin E have been found to antagonize vitamin K (8). Excess vitamin A appears to interfere with vitamin K absorption, whereas vitamin E may inhibit vitamin K-dependent carboxylase activity and interfere with the coagulation cascade (129). One study in adults with normal coagulation status found that supplementation with 1,000 IU/day of vitamin E for 12 weeks decreased γ-carboxylation of prothrombin, a vitamin K-dependent protein (130). Individuals taking anticoagulatory drugs like warfarin and those who are vitamin K deficient should not take vitamin E supplements without close medical supervision because of the increased risk of hemorrhage (excessive bleeding) (131).

Drug interactions

The anticoagulant effect of vitamin K antagonists (e.g., warfarin) may be compromised by very high dietary or supplemental vitamin K intake. Moreover, daily phylloquinone supplements of up to 100 μg are considered safe for patients taking warfarin, but therapeutic anticoagulant stability may be undermined by daily doses of MK-7 as low as 10 to 20 μg (132). It is generally recommended that individuals using warfarin try to consume the AI for vitamin K (90-120 μg/day) and avoid large fluctuations in vitamin K intake that might interfere with the adjustment of their anticoagulant dose (9, 10, 133). The prescription of anti-vitamin K anticoagulants, anticonvulsants (e.g., phenytoin), and anti-tuberculosis drugs (e.g., rifampin and isoniazid) to pregnant or breast-feeding women may place the newborn at increased risk of vitamin K deficiency (134).

The drug amiodarone, used in the management of certain cardiac arrhythmias (irregular heartbeat), including atrial fibrillation, can enhance the anticoagulant effect of warfarin and thus increase the risk of hemorrhage (135, 136). Further, the use of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, mineral oil, and the fat substitute, olestra, may interfere with fat absorption and affect the absorption of fat-soluble vitamins, including vitamin K (137).

Linus Pauling Institute Recommendation

It is not clear whether the AI for vitamin K is enough to optimize the γ-carboxylation of vitamin K-dependent proteins in bone (see Osteoporosis). To consume the amount of vitamin K associated with a decreased risk of hip fracture in the Framingham Heart Study (about 250 μg/day) (50), an individual would need to eat a little more than ½ cup of chopped broccoli or a large salad of mixed greens every day. Though the dietary intake of vitamin K required for optimal function of all vitamin K-dependent proteins is not yet known, the Linus Pauling Institute recommends taking a multivitamin/mineral supplement and eating at least one cup of dark-green leafy vegetables daily. Replacing dietary saturated fats like butter and cheese with monounsaturated fats found in olive oil and canola oil will increase dietary vitamin K intake and may decrease the risk of cardiovascular disease.

Older adults (>50 years)

Because older adults are at increased risk of osteoporosis and hip fracture, the above recommendation for a multivitamin/mineral supplement and at least one cup of dark green leafy vegetables daily is especially relevant.

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Minerals

Español

Minerals are elements that originate in the Earth and cannot be made by living organisms. Plants obtain minerals from the soil, and most of the minerals in our diets come directly from plants or indirectly from animal sources. Minerals may also be present in the water we drink, but this varies with geographic locale. Minerals from plant sources may also vary from place to place, because soil mineral content varies geographically.

The information from the Linus Pauling Institute's Micronutrient Information Center on vitamins and minerals is now available in a book titled, *An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations*. The book can be purchased from the Linus Pauling Institute or Thieme Medical Publishers.

Select a mineral from the list for more information.

- Calcium
- Chromium
- Copper
- Fluoride
- Iodine
- Iron
- Magnesium
- Manganese
- Molybdenum
- Phosphorus
- Potassium
- Selenium
- Sodium (Chloride)
- Zinc

Calcium

Contents

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Español | 日本語

Summary

- Calcium is a major constituent of bones and teeth and also plays an essential role as second messenger in cell-signaling pathways. Circulating calcium concentrations are tightly controlled by the parathyroid hormone (PTH) and vitamin D at the expense of the skeleton when dietary calcium intakes are inadequate. *(More information)*
- The recommended dietary allowance (RDA) for calcium is 1,000 mg/day-1,200 mg/day for adults. *(More information)*
- The skeleton is a reserve of calcium drawn upon to maintain normal serum calcium in case of inadequate dietary calcium. Thus, calcium sufficiency is required to maximize the attainment of peak bone mass during growth and to limit the progressive demineralization of bones later in life, which leads to osteoporosis, bone fragility, and an increased risk of fractures. *(More information)*
- High concentrations of calcium and oxalate in the urine are major risk factors for the formation of calcium oxalate stones in the kidneys. Because dietary calcium intake has been inversely associated with stone occurrence, it is thought that adequate calcium consumption may reduce the absorption of dietary oxalate, thus reducing urinary oxalate and kidney stone formation. *(More information)*
- Data from observational studies and randomized controlled trials support calcium supplementation in reducing the risk of high blood pressure and preeclampsia in pregnant women. The World Health Organization advises that all pregnant women in areas of low calcium intake (i.e., low-income countries with intakes around 300 to 600 mg/day) be given supplemental calcium starting in the 20th week of pregnancy. *(More information)*
- Prospective cohort studies have reported an association between higher calcium intakes and lower risk of developing colorectal cancer; however, large clinical trials of calcium supplementation are needed. *(More information)*
- Current available data suggest that adequate calcium intakes may play a role in body weight regulation and have therapeutic benefits in the management of moderate-to-severe premenstrual symptoms. *(More information)*
- Adequate calcium intake is critical for maintaining a healthy skeleton. Calcium is found in a variety of foods, including dairy products, beans, and vegetables of the kale family. Yet, content and bioavailability vary among foods, and certain drugs are known to adversely affect calcium absorption. *(More information)*
- Hypercalcemia, a condition of abnormally high concentrations of calcium in blood, is usually due to malignancy or primary hyperparathyroidism. However, the use of large doses of supplemental calcium, together with absorbable alkali, increases the risk of hypercalcemia, especially in postmenopausal women. Often associated with gastrointestinal disturbances, hypercalcemia can be fatal if left untreated. *(More information)*
- High calcium intakes — either from dairy foods or from supplements — have been associated with increased risks of prostate cancer and cardiovascular events in some, but not all, observational and intervention studies. However, there is currently no evidence of such detrimental effects when people consume a total of 1,000 to 1,200 mg/day of calcium (diet and supplements combined), as recommended by the Food and Nutrition Board of the Institute of Medicine. *(More information)*

Calcium is the most abundant mineral in the human body. About 99% of the calcium in the body is found in bones and teeth, while the other 1% is found in the blood and soft tissue. Calcium concentrations in the blood and fluid surrounding the cells (extracellular fluid) must be maintained within a narrow concentration range for normal physiological functioning. The physiological functions of calcium are so vital to survival that the body will stimulate bone resorption (demineralization) to maintain normal blood calcium concentrations when calcium intake is inadequate. Thus, adequate intake of calcium is a critical factor in maintaining a healthy skeleton (1).

Function

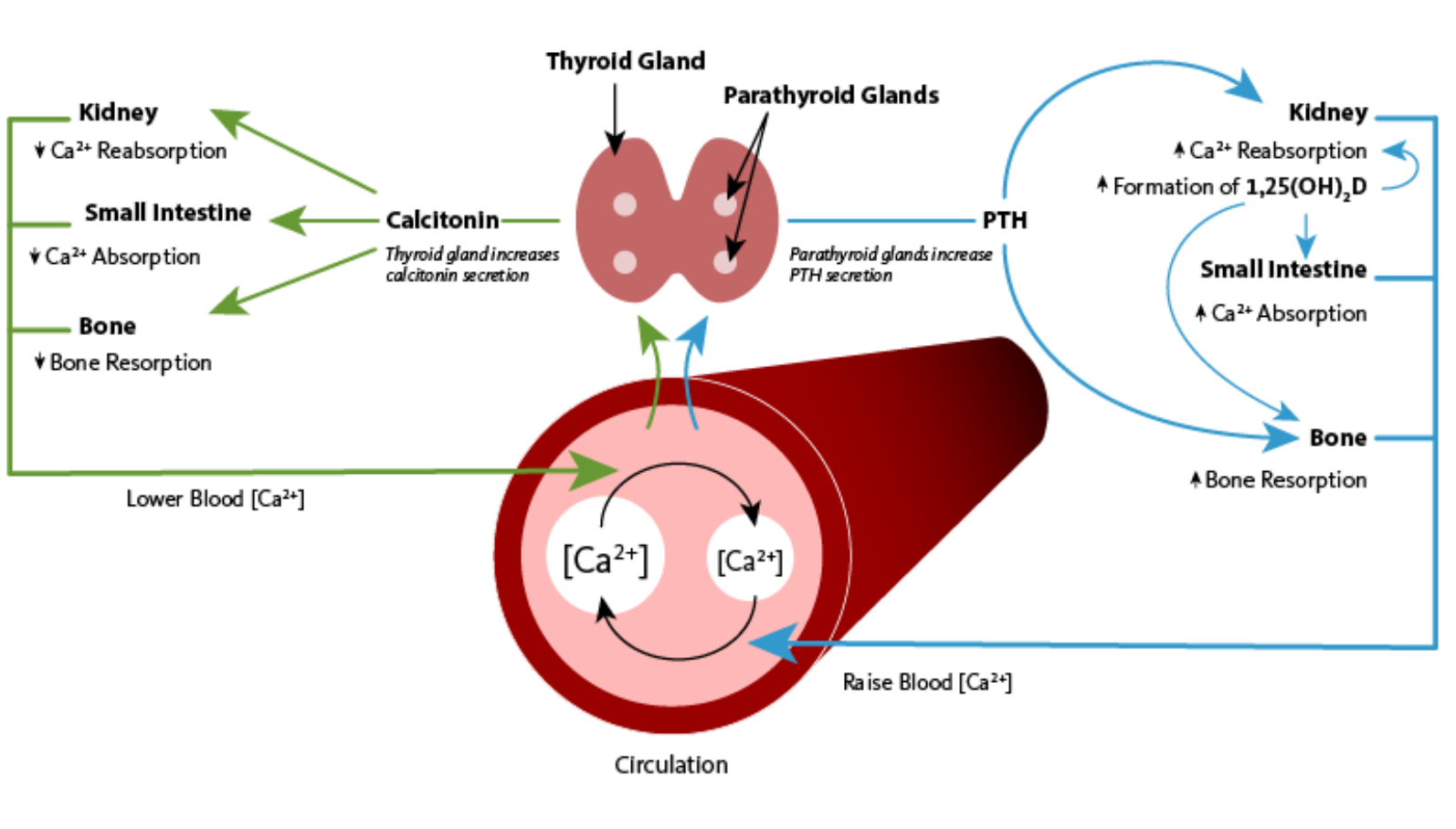
Structure

Calcium is a major structural element in bones and teeth. The mineral component of bone consists mainly of hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ crystals, which contain large amounts of calcium, phosphorus, and oxygen. Bone is a dynamic tissue that is remodeled throughout life. Bone cells called osteoclasts begin the process of remodeling by dissolving or resorbing bone. Bone-forming cells called osteoblasts then synthesize new bone to replace the bone that was resorbed. During normal growth, bone formation exceeds bone resorption. Osteoporosis may result when bone resorption chronically exceeds formation (1).

Calcium homeostasis

Calcium concentrations in the blood and fluid that surround cells are tightly controlled in order to preserve normal physiological function. A slight drop in blood calcium concentration (e.g., in the case of inadequate calcium intake) is sensed by the parathyroid glands, resulting in their increased secretion of parathyroid hormone (PTH). In the kidneys, PTH stimulates the conversion of vitamin D into its active form (1,25-dihydroxyvitamin D; calcitriol), which rapidly decreases urinary excretion of calcium but increases urinary excretion of phosphorus. Elevations in PTH also stimulates bone resorption, resulting in the release of bone mineral (calcium and phosphate) — actions that also contribute to restoring serum calcium concentrations. Increased circulating 1,25-dihydroxyvitamin D also triggers intestinal absorption of both calcium and phosphorus. Like PTH, 1,25-dihydroxyvitamin D stimulates the release of calcium from bone by activating osteoclasts (bone-resorbing cells). When blood calcium rises to normal levels, the parathyroid glands stop secreting PTH. A slight increase in blood calcium concentration stimulates the production and secretion of the peptide hormone, calcitonin, by the thyroid gland. Calcitonin inhibits PTH secretion, decreases both bone resorption and intestinal calcium absorption, and increases urinary calcium excretion (**Figure 1**). Finally, acute changes in blood calcium concentrations do not seem to elicit the secretion of the phosphaturic hormone fibroblast growth factor 23 (FGF-23), which is produced by bone-forming cells (osteoblasts/osteocytes) in response to increases in phosphorus intake (see the article on Phosphorus) (2). While this complex system allows for rapid and tight control of blood calcium concentrations, it does so at the expense of the skeleton (1).

Figure 1. Calcium Homeostasis



[Figure 1 - Click to Enlarge]

Cell signaling

Calcium plays a role in mediating the constriction and relaxation of blood vessels (vasoconstriction and vasodilation), nerve impulse transmission, muscle contraction, and the secretion of hormones like insulin (1). Excitable cells, such as skeletal muscle and nerve cells, contain voltage-dependent calcium channels in their cell membranes that allow for rapid changes in calcium concentrations. For example, when a nerve impulse stimulates a muscle fiber to contract, calcium channels in the cell membrane open to allow calcium ions into the muscle cell. Within the cell, these calcium ions bind to activator proteins, which help release a flood of calcium ions from storage vesicles of the endoplasmic reticulum (ER) inside the cell. The binding of calcium to the protein troponin-c initiates a series of steps that lead to muscle contraction. The binding of calcium to the protein calmodulin activates enzymes that break down muscle glycogen to provide energy for muscle contraction. Upon completion of the action, calcium is pumped outside the cell or into the ER until the next activation (reviewed in 3).

Regulation of protein function

Calcium is necessary to stabilize a number of proteins, including enzymes, optimizing their activities. The binding of calcium ions is required for the activation of the seven "vitamin K-dependent" clotting factors in the coagulation cascade. The term, "coagulation cascade," refers to a series of events, each dependent on the other that stops bleeding through clot formation (see the article on Vitamin K).

Nutrient interactions

Vitamin D

Vitamin D is required for optimal calcium absorption (see Function or the article on Vitamin D). Several other nutrients (and non-nutrients) influence the retention of calcium by the body and may affect calcium nutritional status.

Sodium

Dietary sodium is a major determinant of urinary calcium loss (1). High-sodium intake results in increased loss of calcium in the urine, possibly due to competition between sodium and calcium for reabsorption in the kidneys or by an effect of sodium on parathyroid hormone (PTH) secretion. Every 1-gram (g) increment in sodium (2.5 g of sodium chloride; NaCl salt) excreted by the kidneys has been found to draw about 26.3 milligrams (mg) of calcium into the urine (1). A study conducted in adolescent girls reported that a high-salt diet had a greater effect on urinary sodium and calcium excretion in White compared to Black girls, suggesting differences among ethnic groups (4). In adult women, each extra gram of sodium consumed per day is projected to produce an additional rate of bone loss of 1% per year if all of the calcium loss comes from the skeleton.

A number of cross-sectional and intervention studies have suggested that high-sodium intakes are deleterious to bone health, especially in older women (5). A two-year longitudinal study in postmenopausal women found increased urinary sodium excretion (an indicator of increased sodium intake) to be associated with decreased bone mineral density (BMD) at the hip (6). Another study in 40 postmenopausal women found that adherence to a low-sodium diet (2 g/day) for six months was associated with significant reductions in sodium excretion, calcium excretion, and amino-terminal propeptide of type I collagen, a biomarker of bone resorption. Yet, these associations were only observed in women with elevated baseline urinary sodium excretions (7). Finally, in a randomized, placebo-controlled study in 60 postmenopausal women, potassium citrate supplementation has been found to prevent an increase in calcium excretion induced by the consumption of a high-sodium diet (≥5,000 mg/day of elemental sodium) for four weeks (8).

Protein

Increasing dietary protein intake enhances intestinal calcium absorption, as well as urinary calcium excretion (9). The RDA for protein is 46 grams (g)/day for adult women and 56 g/day for adult men; however, the average intake of protein in the US tends to be higher (about 70 g/day in adult women and over 100 g per day in adult men) (10). It was initially thought that high-protein diets may result in a negative calcium balance (when the sum of urinary and fecal calcium excretion becomes greater than calcium intake) and thus increase bone loss (11). However, most observational studies have reported either no association or positive associations between protein intake and bone mineral density in children, adults, and elderly subjects (reviewed in 12). The overall calcium balance appears to be unchanged by high dietary protein intake in healthy individuals (13), and current evidence suggests that increased protein intakes in those with adequate supplies of protein, calcium, and vitamin D do not adversely affect BMD or fracture risk (14).

Phosphorus

Phosphorus, which is typically found in protein-rich food, tends to increase the excretion of calcium in the urine. Diets with low calcium-to-phosphorus ratios (Ca:P ≤0.5) have been found to increase parathyroid hormone (PTH) secretion and urinary calcium excretion (15, 16). Also, the intestinal absorption and fecal excretion of calcium and phosphorus are influenced by calcium-to-phosphorus ratios of ingested food. Indeed, in the intestinal lumen, calcium salts can bind to phosphorus to form complexes that are excreted in the feces. This forms the basis for using calcium salts as phosphorus binders to lower phosphorus absorption in individuals with kidney insufficiency (17). Increasing phosphorus intakes from cola soft drinks (high in phosphoric acid) and food additives (high in phosphates) may have adverse effects on bone health (18). At present, there is no convincing evidence that the dietary phosphorus levels experienced in the US adversely affect bone health. Yet, the substitution of large quantities of phosphorus-containing soft drinks for milk or other sources of dietary calcium may represent a serious risk to bone health in adolescents and adults (see the article on Phosphorus).

Caffeine

Exposure to caffeine concentrations ≤400 mg/day have led to increased urinary calcium content in two randomized controlled trials (19, 20). However, caffeine intakes of 400 mg/day did not significantly change urinary calcium excretion over 24 hours in premenopausal women when compared to a placebo (21). A systematic review of 14 studies recently concluded that daily intake of ≤400 mg of caffeine was unlikely to interfere with calcium homeostasis, impact negatively bone mineral density, or increase the risks of osteoporosis and fracture in individuals with adequate calcium intakes (22).

Deficiency

A low blood calcium level (hypocalcemia) usually implies abnormal parathyroid function since the skeleton provides a large reserve of calcium for maintaining normal blood levels, especially in the case of low dietary calcium intake. Other causes of abnormally low blood calcium concentrations include chronic kidney failure, vitamin D deficiency, and low blood magnesium levels often observed in cases of severe alcoholism. Magnesium deficiency can impair parathyroid hormone (PTH) secretion by the parathyroid glands and lower the responsiveness of osteoclasts to PTH. Thus, magnesium supplementation is required to correct hypocalcemia in people with low serum magnesium concentrations (see the article on Magnesium). Chronically low calcium intakes in growing individuals may prevent the attainment of optimal peak bone mass. Once peak bone mass is achieved, inadequate calcium intake may contribute to accelerated bone loss and ultimately to the development of osteoporosis (see Disease Prevention) (1).

The Recommended Dietary Allowance (RDA)

Updated recommendations for calcium intake based on the optimization of bone health were released by the Food and Nutrition Board (FNB) of the Institute of Medicine in 2011 (9). The Recommended Dietary Allowance (RDA) for calcium is listed in **Table 1** by life stage and gender.

Table 1. Recommended Dietary Allowance (RDA) for Calcium

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	200 (AI)	200 (AI)
Infants	6-12 months	260 (AI)	260 (AI)
Children	1-3 years	700	700
Children	4-8 years	1,000	1,000
Children	9-13 years	1,300	1,300
Adolescents	14-18 years	1,300	1,300
Adults	19-50 years	1,000	1,000
Adults	51-70 years	1,000	1,200
Adults	>70 years	1,200	1,200
Pregnancy	14-18 years	-	1,300
Pregnancy	19-50 years	-	1,000
Breast-feeding	14-18 years	-	1,300
Breast-feeding	19-50 years	-	1,000

Disease Prevention

Osteoporosis

Osteoporosis is a skeletal disorder in which bone mass and strength are compromised, resulting in an increased risk of fracture. Sustaining a hip fracture is one of the most serious consequences of osteoporosis. Nearly one-third of those who sustain osteoporotic hip fractures enter nursing homes within a year following the fracture, and one person in four dies within one year of experiencing an osteoporotic hip fracture (23). Despite being a common diagnosis in postmenopausal women, osteoporosis also affects 4%-6% of men over the age of 50 years (24).

Osteoporosis is a multifactorial disorder, and nutrition is only one factor contributing to its development and progression (25). Other factors that increase the risk of developing osteoporosis include, but are not limited to, increased age, female gender, estrogen deficiency, smoking, high alcohol intake (three or more drinks/day), metabolic disease (e.g., hyperthyroidism), and the use of certain medications (e.g., corticosteroids and anticonvulsants) (26). A predisposition to osteoporotic fracture is related to one's peak bone mass and to the rate of bone loss after peak bone mass has been attained. After adult height has been reached, the skeleton continues to accumulate bone until the third decade of life. Genetic factors exert a strong influence on peak bone mass, but lifestyle factors can also play a significant role. Strategies for reducing the risk of osteoporotic fracture include the attainment of maximal peak bone mass and the reduction of bone loss later in life. A number of lifestyle factors, including diet (especially calcium and protein intake) and physical activity, are amenable to interventions aimed at maximizing peak bone mass and limiting osteoporotic fracture risk (27).

Physical exercise is a lifestyle factor that has been associated with numerous health benefits and is likely to contribute to the prevention of osteoporosis and osteoporotic fracture. There is evidence to suggest that physical activity early in life contributes to the attainment of higher peak bone mass (27). Moreover, lifelong participation in physical activities in the presence of adequate calcium and vitamin D supply (from dietary sources and/or sunlight exposure) may have a modest effect on slowing the rate of bone loss later in life (28). Current National Osteoporosis Foundation guidelines include recommendations of regular muscle-strengthening and weight-bearing exercise to all postmenopausal women and men ages 50 and older (29). Although benefits in reducing bone loss might be limited, muscle-strengthening exercise, including weight training and other resistive exercises (e.g., yoga and Pilates) and weight-bearing exercise (e.g., walking, jogging, and stair climbing), may improve strength, posture, balance, and coordination, thus contributing to reduced risk of falls (29). One compilation of published calcium trials indicated that the beneficial skeletal effect of increased physical activity was achievable only at calcium intakes above 1,000 mg/day in women in late menopause (reviewed in 28).

The progressive loss of bone mineral density (BMD) leading to osteopenia (pre-osteoporosis) and osteoporosis is usually assessed by dual-energy x-ray absorptiometry (DEXA) at the hip and lumbar spine (30). Several randomized, placebo-controlled clinical trials have evaluated the effect of supplemental calcium in the preservation of BMD and the prevention of fracture risk in men and women aged 50 years and older. A meta-analysis of 15 randomized controlled trials, including 1,533 men and women >50 years of age, found that increasing calcium intake from dietary sources (i.e., milk, milk powder, dairy products, or hydroxyapatite preparations) increased BMD by 0.6%-1% at the hip (+0.6%) and total body (+1.0%) after one year and by 0.7%-1.8% at the lumbar spine (+0.7%), femoral neck (+1.8%), total hip (+1.5%), and total body (+0.9%) sites after two years (31). A meta-analysis of 51 randomized controlled trials in 12,257 adults (>50 years) found that BMD at all bone sites (lumbar spine, femoral neck, total hip, forearm) increased by 0.7%-1.4% after one year and 0.8%-1.5% after two years of supplemental calcium, alone or in combination with vitamin D (31). Such modest increases may help limit the average rate of BMD loss after menopause but are unlikely to translate into meaningful fracture risk reductions. A meta-analysis of 20 randomized controlled trials that reported on total fracture risk found an 11% risk reduction associated with supplemental calcium with or without vitamin D (32). However, there was no effect when the analysis was restricted to the largest trials with the lowest risk of bias. Additionally, no reductions were found in risks of hip, vertebral and forearm fractures with calcium supplementation (32). Because estrogen withdrawal significantly impairs intestinal absorption and renal reabsorption of calcium, the level of calcium requirement might depend on whether postmenopausal women receive hormone replacement therapy (28).

The US Preventive Services Task Force conducted a meta-analysis of 11 randomized placebo-controlled trials that included 52,915 older people (of whom 69% were postmenopausal women) and reported that the supplementation of vitamin D (300-1,000 IU/day) and calcium (500-1,200 mg/day) for up to seven years resulted in a 12% reduction in the risk of any new fracture (33). There was no significant effect of vitamin D without calcium (33). A recently updated meta-analysis of randomized, placebo-controlled trials commissioned by the National Osteoporosis Foundation found a 15% reduction in risk of total fracture (8 studies) and a 30% reduction in risk of hip fractures (six studies) with calcium and vitamin D supplementation in older people (34). The National Osteoporosis Foundation advises that adequate intake of calcium (1,000-1,200 mg/day) and vitamin D (800-1,000 IU/day) be included in the diet of all middle-aged men and women (35).

The role and efficacy of vitamin D supplementation in strengthening bone and preventing fracture in older people remain controversial topics. The active form of vitamin D, 1,25-dihydroxyvitamin D, stimulates calcium absorption by promoting the synthesis of calcium-binding proteins in the intestine. While no amount of vitamin D can compensate inadequate total calcium intake, vitamin D insufficiency (defined as circulating concentrations of 25-hydroxyvitamin D below 20 ng/mL [50 nmol/L]) can lead to secondary hyperparathyroidism and an increased risk of osteoporosis (9, 36). Conversely, in postmenopausal women (ages 57-90 years) with adequate total calcium intakes (1,400 IU/day), serum 25-hydroxyvitamin D concentrations ranging from 20 ng/mL to 66 ng/mL had little effect on calcium absorption (only 6% increase over the range) (37). In a randomized, placebo-controlled trial, the supplementation of 1,000 IU/day of vitamin D to postmenopausal women (mean age, 77.2 years) for one year was found to significantly increase circulating 25-hydroxyvitamin D concentrations by 34% from baseline but failed to enhance calcium absorption in the presence of high total calcium intakes (dietary plus supplemental calcium corresponding to an average 2,100 mg/day) (38). This study also reported no significant difference in measures of BMD at the hip and total body between placebo- and vitamin D-treated women. In addition, the pooled analysis of seven randomized controlled trials, including 65,517 older individuals living in the community or in an institution, found that vitamin D (400-800 IU/day) could reduce the risk of any fracture only when combined with calcium (1,000 mg/day) (39). Interestingly, the results of a series of trials included in three recent meta-analyses (33, 40, 41) have suggested that supplemental vitamin D and calcium may have greater benefits in the prevention of fracture in institutionalized, older people who are also at increased risk of vitamin D deficiency and fractures compared to community dwellers (42, 43).

For more information about bone health and osteoporosis, see the article, Micronutrients and Bone Health, and visit the National Osteoporosis Foundation website.

Kidney stones

Approximately 6% of women and 15% of men in industrialized countries will have a kidney stone during their lifetime. Most kidney stones are composed of calcium oxalate or calcium phosphate. Subjects with an abnormally high level of calcium in the urine (hypercalciuria) are at higher risk of developing kidney stones (a process called nephrolithiasis) (44). High urinary oxalate level is another risk factor for calcium oxalate stone formation. Most subjects with a history of kidney stones and/or idiopathic hypercalciuria have increased intestinal calcium absorption (45). Although it was initially recommended to limit dietary calcium intake in these patients, a number of prospective cohort studies have reported associations between lower total dietary calcium intake and increased risk of incident kidney stones (46-48). The prospective analyses of three large cohorts, including a total of 30,762 men and 195,865 women followed for a combined 56 years, have indicated that the risk of kidney stones was significantly lower in individuals in the highest versus lowest quintile of dietary calcium intake from dairy or nondairy sources (49). Additionally, a five-year randomized intervention study that enrolled 120 men with idiopathic hypercalciuria (mean age, 45 years) reported that those assigned to a low-calcium diet (approximately 400 mg/day) had a 51% higher risk of kidney stone recurrence compared to those on a normal-to-high calcium (1,200 mg/day), low animal-protein, low-salt diet (50).

Mechanisms by which increased dietary calcium might reduce the risk of incident kidney stones are not fully understood. An inverse relationship was reported between total calcium intake and intestinal calcium absorption in the recent cross-sectional analysis of a cohort of 5,452 postmenopausal women (45). Moreover, women with higher supplemental calcium intake and lower calcium absorption were less likely to report a history of kidney stones (45). Adequate intake of calcium with food may reduce the absorption of dietary oxalate and lower urinary oxalate through formation of the insoluble calcium oxalate salt (51, 52). A recent small intervention study in 10 non-stone-forming young adults observed that the ingestion of large amounts of oxalate did not increase the risk of calcium oxalate stone occurrence in the presence of recommended level of dietary calcium (53).

However, a randomized, double-blind, placebo-controlled trial in 36,282 postmenopausal women reported that a combination of supplemental calcium (1,000 mg/day) and vitamin D (400 IU/day) was associated with a significantly increased incidence of self-reported kidney stones during a seven-year treatment period. More controlled trials may be necessary to determine whether supplemental calcium affects kidney stone risk (54). However, a systematic review of observational studies and randomized controlled trials that primarily reported on bone-related outcomes failed to find an effect of calcium supplementation on stone incidence (55). A potential kidney stone risk associated with calcium supplementation may likely depend on whether supplemental calcium is co-ingested with oxalate-containing foods or consumed separately. Further research is needed to verify whether osteoporosis treatment drugs (e.g., biphosphonates) rather than calcium supplements might influence the risk of stone occurrence (56).

Current data suggest that diets providing adequate dietary calcium and low levels of animal protein, oxalate, and sodium may benefit the prevention of stone recurrence in subjects with idiopathic hypercalciuria (57-59).

Hypertensive disorders of pregnancy

Pregnancy-induced hypertensive disorders, including gestational hypertension, preeclampsia, and eclampsia, complicate approximately 10% of pregnancies and are a major health risk for pregnant women and their offspring (60). Gestational hypertension is defined as an abnormally high blood pressure that usually develops after the 20th week of pregnancy. Preeclampsia is characterized by poor placental perfusion and a systemic inflammation that may involve several organ systems, including the cardiovascular system, kidneys, liver, and hematological system (61). In addition to gestational hypertension, preeclampsia is associated with the development of severe swelling (edema) and the presence of protein in the urine (proteinuria). Eclampsia is the occurrence of seizures in association with the syndrome of preeclampsia and is a significant cause of maternal and perinatal mortality.

Although cases of preeclampsia are at high risk of developing eclampsia, one-quarter of women with eclampsia do not initially exhibit preeclamptic symptoms. Risk factors for preeclampsia include genetic predisposition, advanced maternal age, first pregnancies, multiple pregnancies (e.g., twins or triplets), obesity, diabetes, and some autoimmune diseases (61). While the pathogenesis of preeclampsia is not entirely understood, nutrition and especially calcium metabolism appear to play a role. Data from epidemiological studies have suggested an inverse relationship between calcium intake during pregnancy and the incidence of preeclampsia (reviewed in 62). Impairment of calcium metabolism when circulating vitamin D concentration is low and/or when dietary calcium intake is inadequate may contribute to the risk of hypertension during pregnancy.

Secondary hyperparathyroidism (high PTH level) due to vitamin D deficiency in young pregnant women has been associated with high maternal blood pressure and increased risk of preeclampsia (63). The risk for elevated PTH concentration was also found to be increased in vitamin D-sufficient women with low-calcium intakes (<480 mg/day) during pregnancy when compared with adequate-to-high calcium intakes (≥1,000 mg/day) (64). In addition, vitamin D deficiency may trigger hypertension through the inappropriate activation of the renin-angiotensin system (see the article on Vitamin D).

Potential beneficial effects of calcium in the prevention of preeclampsia have been investigated in several randomized, placebo-controlled studies. The most recent meta-analysis of 13 trials in 15,730 pregnant women found that calcium supplementation with at least 1,000 mg/day (mostly 1,500-2,000 mg/day) from about 20 weeks of pregnancy (34 weeks of pregnancy at the latest) was associated with significant reductions in the risk of high blood pressure, preeclampsia, and preterm birth (62). Greater risk reductions were reported among pregnant women at high risk of preeclampsia (5 trials; 587 women) or with low dietary calcium intake (8 trials; 10,678 women). Another meta-analysis of nine randomized controlled trials in high-risk women indicated that lower doses of calcium supplementation (≤800 mg/day), alone or with a co-treatment (i.e., vitamin D, linoleic acid, or antioxidants), could also lower the risk of preeclampsia by 62% (65). Yet, based on the systematic review of high-quality randomized controlled trials, which used mostly high-dose calcium supplements, the World Health Organization (WHO) recently recommended that all pregnant women in areas of low-calcium intake (i.e., low-income countries with intakes around 300-600 mg/day) be given 1.5 to 2 g (1,500 to 2,000 mg)/day of elemental calcium from the 20th week of pregnancy (66).

Because excessive calcium supplementation may be harmful (see Safety), further research is required to verify whether calcium supplementation above the current IOM recommendation (1,000 mg/day for pregnant women, ages 19-50 years) would provide greater benefits to women at high risk of preeclampsia. Finally, the lack of effect of supplemental calcium on proteinuria (reported in two trials only) suggested that calcium supplementation from mid-pregnancy might be too late to oppose the genesis of preeclampsia (67, 68). A randomized, double-blind, placebo-controlled study — the WHO Calcium and Pre-eclampsia (CAP) trial — is ongoing to evaluate the effect of calcium supplementation with 500 mg/day, starting before pregnancy and until the 20th week of pregnancy, on the risk of preeclampsia in high-risk women (69, 70).

Colorectal cancer

Colorectal cancer (CRC) is the most common gastrointestinal cancer and the second leading cause of cancer death in the US (71). CRC is caused by a combination of genetic and environmental factors, but the degree to which these two types of factors influence CRC risk in individuals varies widely. In individuals with familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC), the cause of CRC is almost entirely genetic, while modifiable lifestyle factors, including dietary habits, tobacco use, and physical activities, greatly influence the risk of sporadic (non-hereditary) CRC.

Prospective cohort studies have consistently reported an inverse association between dairy food consumption and CRC risk. Experimental studies in cell culture and animal models have suggested plausible mechanisms underlying a role for calcium, a major nutrient in dairy products, in preventing CRC (72). In the multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study of 477,122 individuals, followed for an average of 11 years, 4,513 CRC cases were documented (73). Intakes of milk, cheese, and yogurt, were inversely associated with CRC risk. The highest versus lowest quintile of total dairy intake (≥490 g/day vs. <134 g/day) was associated with a 23% lower risk of CRC. Similarly, CRC risk was 25% lower in those in the top versus bottom quintile of calcium intake from dairy food (≥839 mg/day vs. <308 mg/day). The 16-year follow-up of 41,403 women (ages 26-46 years at inclusion) from the prospective Nurses' Health Study II (NHS II) documented 2,273 diagnoses of colorectal adenomas (precancerous polyps). The analysis of the prospective cohort found that women with total calcium intake of 1,001-1,250 mg/day had a 76% lower risk of developing advanced adenomas (i.e., adenomas more likely to become malignant) compared to those with intakes equal to and below 500 mg/day (74). In addition, a dose-response analysis using data from eight prospective studies (11,005 CRC cases) estimated that an increase of 300 mg/day in total calcium intake was associated with a 5% reduction in CRC risk (75). Total daily intake of calcium ranged from 333 to 2,229 mg in the examined studies. In addition, the dose-response analysis of six prospective studies (8,839 CRC cases among 920,837 participants) showed 11% lower odds of high-risk adenomas for each 300 mg/day increment in total calcium (75).

However, the meta-analysis of seven randomized, double-blind, placebo-controlled studies found no evidence of an effect of calcium supplementation (≥500 mg/day) for a median period of 45 months on total cancer risk and CRC risk (76). In addition, the re-analysis of the Women's Health Initiative placebo-controlled trial failed to show a reduction in CRC risk in postmenopausal women supplemented with both vitamin D (400 IU/day) and calcium (1,000 mg/day) for seven years (77). Finally, the results of the meta-analysis of four randomized, placebo-controlled trials have suggested that calcium supplementation (1,200-2,000 mg/day) may reduce the risk of adenoma recurrence by 13% over three to five years in subjects with a history of adenomas (78). At present, it is not clear whether calcium supplementation is beneficial in CRC prevention. Larger trials designed to assess primarily the effect of long-term calcium supplementation on the incidence of adenomas and/or CRC are needed before conclusions can be drawn.

Lead toxicity

Children who are chronically exposed to lead, even in small amounts, are more likely to develop learning disabilities, behavioral problems, and to have low IQs. Deficits in growth and neurological development may occur in the infants of women exposed to lead during pregnancy and lactation. In adults, lead toxicity may result in kidney damage and high blood pressure. Although the use of lead in paint products, gasoline, and food cans has been discontinued in the US, lead toxicity continues to be a significant health problem, especially in children living in urban areas (79).

In 2012, the US Centers for Disease Control and Prevention set the reference value for blood lead concentration at 5 micrograms per deciliter (mg/dL) to identify children at risk (80). Yet, there is no known blood lead concentration below which children are 100% safe. An early study of over 300 children in an urban neighborhood found that 49% of children ages 1 to 8 years had blood lead levels above the threshold of 10 mg/dL, indicating excessive lead exposure. In this study, only 59% of children ages 1 to 3 years and 41% of children ages 4 to 8 years met the recommended levels for calcium intakes (81).

Adequate calcium intake could be protective against lead toxicity in at least two ways. Increased dietary intake of calcium is known to decrease the gastrointestinal absorption of lead. Once lead enters the body it tends to accumulate in the skeleton, where it may remain for more than 20 years. Adequate calcium intake also prevents lead mobilization from the skeleton during bone demineralization. A study of circulating concentrations of lead during pregnancy found that women with inadequate calcium intake during the second half of pregnancy were more likely to have elevated blood lead levels, probably because of increased bone demineralization, leading to the release of accumulated lead into the blood (82). Lead in the blood of a pregnant woman is readily transported across the placenta resulting in fetal lead exposure at a time when the developing nervous system is highly vulnerable. In a randomized, double-blind, placebo-controlled study in 670 pregnant women (≤14 weeks' gestation) with average dietary calcium intakes of 900 mg/day, daily supplementation of 1,200 mg of calcium throughout the pregnancy period resulted in 8%-14% reductions in maternal blood lead concentrations (83). Similar reductions in maternal lead concentrations in the blood and breast milk of lactating mothers supplemented with calcium were reported in earlier trials (84, 85). In postmenopausal women, factors known to decrease bone demineralization, including estrogen replacement therapy and physical activity, have been inversely associated with blood lead levels (86).

Disease Treatment

Overweight and obesity

High dietary calcium intake, usually associated with dairy product consumption, has been inversely related to body weight and central obesity in a number of cross-sectional studies (reviewed in 87). Cross-sectional baseline data analyses of a number of prospective cohort studies that were not designed and powered to examine the effect of calcium intake or dairy consumption on obesity or body fat have given inconsistent results (87). Yet, a meta-analysis of 18 cross-sectional and prospective studies predicted a reduction in body mass index (a relative measure of body weight; BMI) of 1.1 kg/m^2 with an increase in calcium intake from 400 mg/day to 1,200 mg/day (87). In a placebo-controlled intervention study, 32 obese subjects were randomized to energy restriction regimens (500 kCal/day deficit) for 24 weeks with (1) a standard diet providing 400 to 500 mg/day of dietary calcium and a placebo ("low calcium" diet), (2) a standard diet and 800 mg/day of supplemental calcium ("high calcium" diet), or (3) a high-dairy diet providing 1,200 mg/day of dietary calcium and a placebo (88). Energy-restricted diets resulted in significant body weight and fat loss in all three groups. Yet, body weight and fat loss were significantly more reduced with the high-calcium diet compared to the standard diet, and further reductions were measured with the high-dairy diet compared to both high-calcium and low-calcium diets. These results suggested that while calcium intake may play a role in body weight regulation, additional benefits might be attributable to other bioactive components of dairy products, such as proteins, fatty acids, and branched chain amino acids.

Yet, several mechanisms have been proposed to explain the potential impact of calcium on body weight (reviewed in 87). The most-cited mechanism is based on studies in the agouti mouse model showing that low-calcium intakes, through increasing circulating parathyroid hormone (PTH) and vitamin D, could stimulate the accumulation of fat (lipogenesis) in adipocytes (fat cells) (89). Conversely, higher intakes of calcium may reduce fat storage, stimulate the breakdown of lipids (lipolysis), and drive fat oxidation. A recent meta-analysis of randomized controlled trials estimated that high (1,300 mg/day) versus low (488 mg/day) calcium intake for a minimum of seven days increased fat oxidation by 11% (90). However, a double-blind, placebo-controlled, randomized, cross-over trial in 10 low-calcium consuming overweight or obese individuals reported that the supplementation with 800 mg/day of calcium for 5 weeks failed to modify the expression of key factors involved in fat metabolism (91). Moreover, while the model suggests a role for vitamin D in lipogenesis (fat storage), human studies have shown that vitamin D deficiency — rather than sufficiency — is often associated with obesity, and supplemental vitamin D might be effective in lowering body weight when caloric restriction is imposed (92, 93). Another mechanism suggests that high-calcium diets may limit dietary fat absorption in the intestine and increase fecal fat excretion. Indeed, in the gastrointestinal tract, calcium may trap dietary fat into insoluble calcium soaps of fatty acids that are then excreted (94). In addition, despite very limited evidence, it has also been proposed that calcium might be involved in regulating appetite and energy intake (95).

To date, there is no consensus regarding the effect of calcium on body weight changes. A meta-analysis of 29 randomized controlled trials in 2,441 participants (median age, 41.4 years) found that calcium supplementation was only associated with body weight and fat loss in short-term studies (<1 year) that used energy-restricted diets (96). Another meta-analysis of 41 randomized controlled trials (4,802 participants) found little-to-no effect of increased calcium intake from supplements or dairy foods for >12 weeks on body weight and body composition (97). Finally, a meta-analysis of 33 randomized controlled trials (4,733 participants) found no overall effect of calcium supplementation (from food or supplements) for >12 weeks on body weight changes. Yet, further subgroup analyses showed weight reductions in children and adolescents (mean, -0.26 kg), in adults (mean, -0.91 kg), and in those with normal BMI (mean, -0.53 kg). Supplemental calcium did not lead to weight loss in postmenopausal women or in overweight/obese individuals (98). At present, additional research is warranted to examine the effect of calcium intake on fat metabolism, as well as its potential benefits in the management of body weight with or without caloric restriction (99).

Premenstrual Syndrome (PMS)

PMS refers to a cluster of symptoms, including but not limited to fatigue, irritability, moodiness/depression, fluid retention, and breast tenderness, that begins sometime after ovulation (mid-cycle) and subsides with the onset of menstruation (the monthly period) (100). A severe form of PMS called premenstrual dysphoric disorder (PMDD) has been described in 3%-8% of women of childbearing age. PMDD interferes with normal functioning, affecting daily activities and relationships (101).

Low dietary calcium intakes have been linked to PMS in early reports, and supplemental calcium has been shown to decrease symptom severity (102). A nested case-control study within the Nurses' Health Study II (NHS II) found that women in the highest quintile of dietary (but not supplemental) calcium intake (median of 1,283 mg/day) had a 30% lower risk of developing PMS compared to those in the lowest quintile (median of 529 mg/day). Similarly, women in the highest versus lowest quintile of skim or low-fat milk intake (≥4 servings/day vs. ≤1 serving/week) had a 46% lower risk of PMS (103). In a randomized, double-blind, placebo-controlled clinical trial of 466 women with moderate-to-severe premenstrual symptoms, supplemental calcium (1,200 mg/day) for three menstrual cycles was associated with a 48% reduction in total symptom scores, compared to a 30% reduction observed in the placebo group (104). Similar positive effects were reported in earlier double-blind, placebo-controlled, cross-over trials that administered 1,000 mg of calcium daily (105, 106). Recent small randomized controlled trials also reported that supplemental calcium (400-500 mg/day) for three weeks to three months reduced severity and/or frequency of symptoms in women with mild-to-moderate PMS (107-110). Currently available data indicate that daily calcium intakes from food and/or supplements may have therapeutic benefits in women diagnosed with PMS or PMDD (111, 112).

Hypertension

The relationship between calcium intake and blood pressure has been investigated extensively over the past decades. A meta-analysis of 23 large observational studies conducted in different populations worldwide found a reduction in systolic blood pressure of 0.34 millimeters of mercury (mm Hg) per 100 mg of calcium consumed daily and a reduction in diastolic blood pressure of 0.15 mm Hg per 100 mg calcium (113). In the DASH (Dietary Approaches to Stop Hypertension) study, 549 people were randomized to one of three diets for eight weeks: (1) a control diet that was low in fruit, vegetables, and dairy products; (2) a diet rich in fruit (~5 servings/day) and vegetables (~3 servings/day); and (3) a combination diet rich in fruit and vegetables, as well as low-fat dairy products (~3 servings/day) (114). The combination diet represented an increase of about 800 mg of calcium/day over the control and fruit/vegetable-rich diets for a total of about 1,200 mg of calcium/day. Overall, the reduction in systolic blood pressure was greater with the combination diet than with the fruit/vegetable diet or the control diet. Among participants diagnosed with hypertension, the combination diet reduced systolic blood pressure by 11.4 mm Hg and diastolic pressure by 5.5 mm Hg more than the control diet, while the reduction for the fruit/vegetable diet was 7.2 mm Hg for systolic and 2.8 mm Hg for diastolic blood pressure compared to the control diet (115). This research suggested that calcium intake at the recommended level (1,000-1,200 mg/day) may be helpful in preventing and treating moderate hypertension (116).

Yet, two large systematic reviews and meta-analyses of randomized controlled trials have examined the effect of calcium supplementation on blood pressure compared to placebo in either normotensive or hypertensive individuals (117, 118). Neither of the analyses reported any significant effect of supplemental calcium on blood pressure in normotensive subjects. A small but significant reduction in systolic blood pressure, but not in diastolic blood pressure, was reported in participants with hypertension. Of note, calcium supplementation in these randomized controlled trials ranged from 400 to 2,200 mg/day, with 1,000 to 1,500 mg/day being the more common dosages. A more recent meta-analysis of 13 randomized controlled studies in 485 individuals with elevated blood pressure found a significant reduction of 2.5 mm Hg in systolic blood pressure but no change in diastolic blood pressure with calcium supplementation (119). The modest effect of calcium on blood pressure needs to be confirmed in larger, high-quality, well-controlled trials before any recommendation is made regarding the management of hypertension. Finally, a review of the literature on the effect of high-calcium intake (dietary and supplemental) in postmenopausal women found either no reduction or mild and transient reductions in blood pressure (120).

More information about the DASH diet is available from the National Institutes of Health (NIH).

Sources

Food sources

Data analysis of the US National Health and Nutrition Examination Surveys (NHANES) 2009-2010 and 2011-2012 found inadequate calcium intakes (defined as intakes below the Estimated Average Requirement [EAR]) in 37.7% of non-supplemented adults (ages, ≥19 years) and 19.6% of adults taking multivitamin/mineral supplements (121). Dairy foods provide 75% of the calcium in the American diet. However, it is typically during the most critical period for peak bone mass development that adolescents tend to replace milk with soft drinks (122). Dairy products represent rich and absorbable sources of calcium, but certain vegetables and grains also provide calcium.

However, the bioavailability of the calcium must be taken into consideration. The calcium content in calcium-rich plants in the kale family (broccoli, bok choy, cabbage, mustard, and turnip greens) is as bioavailable as that in milk; however, other plant-based foods contain components that inhibit the absorption of calcium. Oxalic acid, also known as oxalate, is the most potent inhibitor of calcium absorption and is found at high concentrations in spinach and rhubarb and somewhat lower concentrations in sweet potatoes and dried beans. Phytic acid (phytate) is a less potent inhibitor of calcium absorption than oxalate. Yeast possess an enzyme (phytase) that breaks down phytate in grains during fermentation, lowering the phytate content of breads and other fermented foods. Only concentrated sources of phytate, such as wheat bran or dried beans, substantially reduce calcium absorption (123).

Additional dietary constituents may affect calcium absorption (see Nutrient interactions). **Table 2** lists a number of calcium-rich foods, along with their calcium content. For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Calcium

Food	Serving	Calcium (mg)
Tofu prepared with calcium sulfate (raw)	½ cup	434
Yogurt, plain, low-fat	8 ounces	415
Sardines, canned	3.75 ounces (1 can)	351
Cheddar cheese	1.5 ounces	303
Milk	8 ounces	300
White beans (cooked)	½ cup	81
Chinese cabbage (Bok choy/Pak choi, cooked)	½ cup	79
Figs (dried)	¼ cup	61
Orange	1 medium	60
Kale (cooked)	½ cup	47
Pinto beans (cooked)	½ cup	39
Broccoli (cooked)	½ cup	31
Red beans (cooked)	½ cup	25

Supplements

Most experts recommend obtaining as much calcium as possible from food because calcium in food is accompanied by other important nutrients that assist the body in utilizing calcium. However, calcium supplements may be necessary for those who have difficulty consuming enough calcium from food (124). No multivitamin/mineral tablet contains 100% of the recommended daily value (DV) for calcium because it is too bulky, and the resulting pill would be too large to swallow. The "Supplement Facts" label, required on all supplements marketed in the US, lists the calcium content of the supplement as elemental calcium. Calcium preparations used as supplements include calcium carbonate, calcium citrate, calcium citrate malate, calcium lactate, and calcium gluconate. To determine which calcium preparation is in your supplement, you may have to look at the ingredient list. Calcium carbonate is generally the most economical calcium supplement. To maximize absorption, take no more than 500 mg of elemental calcium at one time. Most calcium supplements should be taken with meals, although calcium citrate and calcium citrate malate can be taken anytime. Calcium citrate is the preferred calcium formulation for individuals who lack stomach acids (achlorhydria) or those treated with drugs that limit stomach acid production (H_2 blockers and proton-pump inhibitors) (reviewed in 125).

Lead in calcium supplements

Several decades ago, concern was raised regarding lead concentrations in calcium supplements obtained from natural sources (oyster shell, bone meal, dolomite) (126). In 1993, investigators found measurable quantities of lead in most of the 70 different preparations they tested (127). Since then, manufacturers have reduced the amount of lead in calcium supplements to less than 0.5 micrograms (mg)/1,000 mg of elemental calcium (128). The US Food and Drug Administration (FDA) has developed provisional total tolerable intake levels (PTTI) for lead for specific age and sex groups (129). Because lead is so widespread and long lasting, no one can guarantee entirely lead-free food or supplements. A study found measurable lead in 8 out of 21 supplements, in amounts averaging 1 to 2 mg/1,000 mg of elemental calcium, which is below the tolerable limit of 7.5 mg/1,000 mg of elemental calcium (130). A more recent survey of 324 multivitamin/mineral supplements labeled for use in children or women found that most supplements would result in lead exposure ranging from 1%-4% of the PTTI (131).

Calcium inhibits intestinal absorption of lead, and adequate calcium intake is protective against lead toxicity, so trace amounts of lead in calcium supplementation may pose less of a risk of excessive lead exposure than inadequate calcium consumption. While most calcium sources today are relatively safe, look for supplements approved or certified by independent testing (e.g., US Pharmacopeia, ConsumerLab.com) (125), follow label instructions, and avoid large doses of supplemental calcium (≥1,500 mg/day).

Safety

Toxicity

Malignancy and primary hyperparathyroidism are the most common causes of elevated calcium concentrations in the blood (hypercalcemia) (132). Hypercalcemia has not been associated with the over consumption of calcium occurring naturally in food. Hypercalcemia has been initially reported with the consumption of large quantities of calcium supplements in combination with antacids, particularly in the days when peptic ulcers were treated with large quantities of milk, calcium carbonate (antacid), and sodium bicarbonate (absorbable alkali). This condition is termed calcium-alkali syndrome (formerly known as milk-alkali syndrome) and has been associated with calcium supplement levels from 1.5 to 16.5 g/day for 2 days to 30 years. Since the treatment for peptic ulcers has evolved and because of the widespread use of over-the-counter calcium supplements, the demographic of this syndrome has changed in that those at greater risk are now postmenopausal women, pregnant women, transplant recipients, patients with bulimia, and patients on dialysis, rather than men with peptic ulcers (reviewed in 133). Supplementation with calcium (0.6 g/day-2 g/day for two to five years) has been associated with a higher risk of adverse gastrointestinal events like constipation, cramping, bloating, pain, diarrhea (134). Mild hypercalcemia may be without symptoms or may result in loss of appetite, nausea, vomiting, constipation, abdominal pain, fatigue, frequent urination (polyuria), and hypertension (132). More severe hypercalcemia may result in confusion, delirium, coma, and if not treated, death (1).

In 2011, the Food and Nutrition Board of the Institute of Medicine updated the tolerable upper intake level (UL) for calcium (9). The UL is listed in **Table 3** by age group.

Table 3. Tolerable Upper Intake Level (UL) for Calcium

Age Group	UL (mg/day)
Infants 0-6 months	1,000
Infants 6-12 months	1,500
Children 1-8 years	2,500
Children 9-13 years	3,000
Adolescents 14-18 years	3,000
Adults 19-50 years	2,500
Adults 51 years and older	2,000

Although the risk of forming kidney stones is increased in individuals with abnormally elevated urinary calcium (hypercalciuria), this condition is not usually related to calcium intake, but rather to increased absorption of calcium in the intestine or increased excretion by the kidneys (9). Overall, increased dietary calcium intake has been associated with a decreased risk of kidney stones (see Kidney stones). Concerns have also been raised regarding the risks of prostate cancer and vascular disease with high intakes of calcium.

Do high calcium intakes increase the risk for prostate cancer?

Prostate cancer is the second most common cancer in men worldwide (135). Several observational studies have raised concern that high-dairy intakes are associated with increased risk of prostate cancer (136-138).

The analysis of a prospective cohort study (2,268 men followed for nearly 25 years) conducted in Iceland, a country with a high incidence of prostate cancer, found a positive association between the consumption of milk (at least once daily) during adolescence and developing prostate cancer later in life (139). Another large prospective cohort study in the US followed 21,660 male physicians for 28 years and found that men with daily skim or low-fat milk intake of at least 237 mL (8 oz) had a higher risk of developing prostate cancer compared to occasional consumers (140). The risk of low-grade, early-stage prostate cancer was associated with higher intake of skim milk, and the risk of developing fatal prostate cancer was linked to the regular consumption of whole milk (140). In a cohort of 3,918 male health professionals diagnosed with prostate cancer, 229 men died of prostate cancer and 69 developed metastasized prostate cancer during a median follow-up of 7.6 years (141). The risk of prostate cancer death was found to be increased in men with high (>4 servings/week) versus low (≤3 servings/month) intakes of whole milk. Yet, no increase in risk of prostate cancer-related mortality was associated with consumption of skim and low-fat milk, total milk, low-fat dairy products, full-fat dairy products, or total dairy products (141). A recent meta-analysis of 32 prospective cohort studies found high versus low intakes of total dairy product (15 studies), total milk (15 studies), whole milk (6 studies), low-fat milk (5 studies), cheese (11 studies), and dairy calcium (7 studies) to be associated with modest, yet significant, increases in the risk of developing prostate cancer (142). However, there was no increase in prostate cancer risk with nondairy calcium (4 studies) and calcium from supplements (8 studies). Moreover, high dairy intakes were not linked to fatal prostate cancer (142).

There is some evidence to suggest that milk consumption may result in higher circulating concentrations of insulin-like growth factor-I (IGF-I), a protein known to regulate cell proliferation (143). Circulating IGF-I concentrations have been positively correlated to the risk of developing prostate cancer in a recent meta-analysis of observational studies (144). Milk-borne IGF-I, as well as dairy proteins and calcium, may contribute to increasing circulating IGF-I in milk consumers (143). In the large EPIC study, which examined the consumption of dairy products in relation to cancer in 142,520 men, the risk of prostate cancer was found to be significantly higher in those in the top versusbottom quintile of both protein and calcium intakes from dairy foods (145). Another mechanism underlying the potential relationship between calcium intake and prostate cancer proposed that high levels of dietary calcium may lower circulating concentrations of 1,25-dihydroxyvitamin D, the active form of vitamin D, thereby suppressing vitamin D-mediated cell differentiation (146). However, studies to date have provided little evidence to suggest that vitamin D status can modify the association between dairy calcium and risk of prostate cancer development and progression (147-149).

In a multicenter, double-blind, placebo-controlled trial, 672 healthy men (mean age of 61.8 years) were randomized to daily calcium supplementation (1,200 mg) for four years. While no increase in the risk for prostate cancer has been reported during a 10.3-year follow-up, calcium supplementation resulted in a significant risk reduction in the period spanning from two years after treatment started to two years after treatment ended (150). In a review of the literature published in 2009, the US Agency for Healthcare Research and Quality indicated that not all epidemiological studies found an association between calcium intake and prostate cancer (151). The review reported that 6 out of 11 observational studies failed to find statistically significant positive associations between prostate cancer and calcium intake. Yet, in five studies, daily intakes of 921 to 2,000 mg of calcium were found to be associated with an increased risk of developing prostate cancer when compared to intakes ranging from 455 to 1,000 mg/day (151). Inconsistencies among studies suggest complex interactions between the risk factors for prostate cancer, as well as reflect the difficulties of assessing the effect of calcium intake in free-living individuals. For example, the fact that individuals with higher dairy and/or calcium intakes were found to be more likely to be engaged in healthy lifestyles or more likely to seek medical attention can mitigate the statistical significance of an association with prostate cancer risk (152). Until the relationship between calcium and prostate cancer is clarified, it is reasonable for men to consume a total of 1,000 to 1,200 mg/day of calcium (diet and supplements combined), which is recommended by the Food and Nutrition Board of the Institute of Medicine (see RDA) (9).

Do calcium supplements increase the risk for cardiovascular disease?

Several observational studies and randomized controlled trials have raised concerns regarding the potential adverse effects of calcium supplements on cardiovascular risk. The analysis of data from the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) prospective study found that users of calcium supplements amongst 10,555 Finnish women (ages 52-62 years) had a 14% greater risk of developing coronary artery disease compared to non-supplement users during a mean follow-up of 6.75 years (153). The prospective study of 23,980 participants (35-64 years old) of the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition cohort (EPIC-Heidelberg) observed that supplemental calcium intake was positively associated with the risk of myocardial infarction (heart attack) but not with the risk of stroke or cardiovascular disease (CVD)-related mortality after a mean follow-up of 11 years (154). Yet, the use of calcium supplements (≥400 mg/day vs. 0 mg/day) was associated with an increased risk of CVD-related mortality in 219,059 men, but not in 169,170 women, included in the National Institute of Health (NIH)-AARP Diet and Health study and followed for a mean period of 12 years. CVD mortality in men was also found to be significantly higher with total (dietary plus supplemental) calcium intakes of 1,500 mg/day and above (155).

In addition, the secondary analyses of two randomized placebo-controlled trials initially designed to assess the effect of calcium on bone health outcomes also suggested an increased risk of CVD in participants daily supplemented with 1,000 mg of calcium for five to seven years (156, 157). In the Auckland Calcium Study of 1,471 healthy postmenopausal women (ages ≥55 years), calcium supplementation resulted in increased risks of myocardial infarction and of a composite cardiovascular endpoint, including myocardial infarction, stroke, or sudden death (156). The analysis of data from 36,282 healthy postmenopausal women randomized to receive a combination of calcium (1,000 mg/day) and vitamin D (400 IU/day) or a placebo in the Women's Health Initiative/Calcium-Vitamin D supplementation study (WHI/CaD study) initially reported no adverse effect on any cardiovascular endpoints with calcium (and vitamin D) compared to placebo (158). A re-analysis was performed with data from 16,718 women who did not take personal calcium supplements (outside protocol) during the five-year study (157). Although criticized on the approach taken (134, 159), the investigators estimated that women supplemented with calcium and vitamin D had a 16% increased risk of clinical myocardial infarction or stroke and a 21% increased risk of myocardial infarction compared to those who received a placebo (157). However, in another randomized, double-blind, placebo-controlled trial — the Calcium Intake Fracture Outcome (CAIFOS) study — in elderly women (median age, 75.1 years), the supplementation of 1,200 mg/day of calcium for five years was not found to increase the risk of vascular disease or related mortality (160). The WHI/CaD data re-analysis also failed to show an increased risk of mortality due to myocardial infarction or coronary artery disease with calcium therapy (156). Also, after an additional follow-up of 4.5 years at the end of the treatment period in the CAIFOS trial, the investigators reported fewer cases of heart failure-related deaths with supplemental calcium compared to placebo (160). In another randomized, placebo-controlled trial of calcium and/or vitamin D_3 (RECORD trial), the evaluation of the effect of 1,000 mg/day of calcium (alone or with 800 IU/day of vitamin D) reported no significant increase in the rate of mortality due to vascular disease in 5,292 participants ages 70 years and older (161). A recent cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III) evaluated the association between calcium intakes and cardiovascular mortality in 18,714 adults with no history of heart disease. No evidence of an association was observed between dietary calcium intake, supplemental calcium intake, or total calcium intake and cardiovascular mortality in either men or women (162).

A few prospective studies have reported positive correlations between high calcium concentrations in the blood and increased rates of cardiovascular events (163, 164). Because supplemental calcium may have a greater effect than dietary calcium on circulating calcium concentrations (see Toxicity), it has been speculated that the use of calcium supplements might promote vascular calcification — a surrogate marker of the burden of atherosclerosis and a major risk factor for cardiovascular events — by raising calcium serum concentrations. In 1,471 older women from the Auckland Calcium Study and 323 healthy older men from another randomized, placebo-controlled trial of daily calcium supplementation (600 mg or 1,200 mg) for two years, serum calcium concentrations were found to be positively correlated with abdominal aortic calcification or coronary artery calcification (165). However, there was no effect of calcium supplementation on measures of vascular calcification scores in men or women. Data from 1,201 participants of the Framingham Offspring study were also used to assess the relationship between calcium intake and vascular calcification. Again, no association was found between coronary calcium scores and total, dietary, or supplemental calcium intake in men or women (166). Nonetheless, in the Multi-Ethnic Study of Atherosclerosis (MESA), a US multicenter prospective study in 6,814 participants followed for a mean 10 years, the greatest risk of developing coronary artery calcification was found in supplement users with the lowest total calcium intake (~306 mg/day of dietary calcium and ~91 mg/day of supplemental calcium), when compared to supplement users with higher total calcium intakes and nonusers (167). Finally, an assessment of atherosclerotic lesions in the carotid artery wall of 1,103 participants in the CAIFOS trial was also conducted after three years of supplementation (168). When compared with placebo, calcium supplementation showed no effect on carotid artery intimal medial thickness (CIMT) and carotid atherosclerosis. Yet, carotid atherosclerosis (but not CIMT) was significantly reduced in women in the highest versus lowest tertile of total (diet and supplements) calcium intakes (≥1,795 mg/day vs. <1,010 mg/day) (168).

The most recent meta-analysis of 18 randomized clinical trials, including a total of 63,563 postmenopausal women, found no evidence of an increased risk for coronary artery disease and all-cause mortality with calcium (≥500 mg/day) supplementation for at least one year (169). Because these clinical trial data are limited to analyses of secondary endpoints, meta-analyses should be interpreted with caution. There is a need for studies designed to examine the effect of calcium supplements on CVD risk as a primary outcome before definite conclusions can be drawn. Based on an updated review of the literature that included four randomized controlled trials, one nested case-control study, and 26 prospective cohort studies (170), the National Osteoporosis Foundation (NOF) and the American Society for Preventive Cardiology (ASPC) concluded that the use of supplemental calcium for generally healthy individuals was safe from a cardiovascular health standpoint when total calcium intakes did not exceed the UL (171). NOF and ASPC support the use of calcium supplements to correct shortfalls in dietary calcium intake and meet current recommendations (171).

Drug interactions

Taking calcium supplements in combination with thiazide diuretics (e.g., hydrochlorothiazide) increases the risk of developing hypercalcemia due to increased reabsorption of calcium in the kidneys. High doses of supplemental calcium could increase the likelihood of abnormal heart rhythms in people taking digoxin (Lanoxin) for heart failure (172). Calcium, when provided intravenously, may decrease the efficacy of calcium channel blockers (173). However, dietary and oral supplemental calcium do not appear to affect the action of calcium channel blockers (174). Calcium may decrease the absorption of tetracycline, quinolone class antibiotics, bisphosphonates, sotalol (a β-blocker), and levothyroxine; therefore, it is advisable to separate doses of these medications and calcium-rich food or supplements by two hours before calcium or four-to-six hours after calcium (175). Supplemental calcium can decrease the concentration of dolutegravir (Tivicay), elvitegravir (Vitekta), and raltegravir (Isentress), three antiretroviral medications, in blood such that patients are advised to take them two hours before or after calcium supplements (175). Intravenous calcium should not be administrated within 48 hours following intravenous ceftriaxone (rocephine), a cephalosporin antibiotic, since a ceftriaxone-calcium salt precipitate can form in the lungs and kidneys and be a cause of death (175). Use of H_2 blockers (e.g., cimetidine) and proton-pump inhibitors (e.g., omeprazole) may decrease the absorption of calcium carbonate and calcium phosphate (reviewed in 176, 177), whereas lithium may increase the risk of hypercalcemia in patients (175). The topical use of calcipotriene, a vitamin D analog, in the treatment of psoriasis places patients at risk of hypercalcemia if they take calcium supplements.

Calcium-nutrient interactions

The presence of calcium decreases iron absorption from nonheme sources (i.e., most supplements and food sources other than meat). However, calcium supplementation up to 12 weeks has not been found to change iron nutritional status, probably due to a compensatory increase in iron absorption (1). Individuals taking iron supplements should take them two hours apart from calcium-rich food or supplements to maximize iron absorption. Although high calcium intakes have not been associated with reduced zinc absorption or zinc nutritional status, an early study in 10 men and women found that 600 mg of calcium consumed with a meal halved the absorption of zinc from that meal (see the article on Zinc) (178). Supplemental calcium (500 mg calcium carbonate) has been found to prevent the absorption of lycopene (a nonprovitamin A carotenoid) from tomato paste in 10 healthy adults randomized into a cross-over study (179).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the recommended dietary allowance (RDA) set by the Food and Nutrition Board of the Institute of Medicine. Following these recommendations should provide adequate calcium to promote skeletal health and may also decrease the risks of some chronic diseases.

Children and adolescents (9-18 years)

To promote the attainment of maximal peak bone mass, children and adolescents should consume a total (diet plus supplements) of 1,300 mg/day of calcium.

Adults (women: 19-50 years; men: 19-70 years)

After adult height has been reached, the skeleton continues to accumulate bone until the third decade of life when peak bone mass is attained. To promote the attainment of maximal peak bone mass and to minimize bone loss later in life, adult women (50 years of age and younger) and adult men (70 years of age and younger) should consume a total (diet plus supplements) of 1,000 mg/day of calcium.

Older women (>50 years)

To minimize bone loss, postmenopausal women should consume a total (diet plus supplements) of 1,200 mg/day of calcium. Taking a multivitamin/mineral supplement containing at least 10 μg (400 IU)/day of vitamin D will help to ensure adequate calcium absorption (see the article on Vitamin D).

Older men (>70 years)

To minimize bone loss, older men should consume a total (diet plus supplements) of 1,200 mg/day of calcium. Taking a multivitamin/mineral supplement containing at least 10 μg (400 IU)/day of vitamin D will help to ensure adequate calcium absorption (see the article on Vitamin D).

Pregnant and breast-feeding women

Pregnant and breast-feeding adolescents (<19 years) should consume a total of 1,300 mg/day of calcium, while pregnant and breast-feeding adults (≥19 years) should consume a total of 1,000 mg/day of calcium.

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Chromium

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Summary

- Chromium (Cr^{0}) is a ubiquitous trace metal. The predominant chromium form in the body is trivalent chromium (Cr^{3+}), which may potentiate insulin function when provided at pharmacological doses. *(More information)*
- The nutritional essentiality of chromium has been questioned, as a dietary deficiency has not been described. In 2001, the US Institute of Medicine set the adequate intake (AI) of chromium at 20-35 μg/day for adults. However, in 2014 the European Food Safety Authority concluded that requirements for chromium could not be established. *(More information)*
- Results of randomized controlled trials of chromium supplementation in the prevention or treatment of impaired glucose tolerance and type 2 diabetes mellitus have been mixed, with few finding benefits that may be clinically meaningful. *(More information)*
- Evidence that supplemental chromium can help treat metabolic syndrome or polycystic ovary syndrome is largely lacking. *(More information)*
- A well-balanced diet that includes fruit, vegetables, meat, fish, and grains should easily cover dietary needs of chromium. *(More information)*
- Few adverse events have been reported with chromium supplementation. *(More information)*

Chromium was first discovered in 1797. The most stable oxidation state of chromium in biological systems is trivalent chromium (Cr^{3+}), which forms relatively inert complexes with proteins and nucleic acids (1). The essentiality of trivalent chromium is questioned, and its proposed function in the body remains poorly understood. In fact, in 2014 the European Food Safety Authority concluded that a dietary requirement — or even an Adequate Intake — cannot be set for trivalent chromium as no conclusive evidence exists that chromium is essential at any dietary intake (2). Trivalent chromium appears to have health effects only at pharmacological doses (reviewed in 3), and a dietary deficiency of the mineral has not been observed.

Another common and stable form of chromium in the environment is hexavalent chromium (Cr^{6+}). Hexavalent chromium is derived from trivalent chromium by heating at alkaline pH and is used as a source of chromium for industrial purposes. Hexavalent chromium is highly toxic and is classified as a human carcinogen when inhaled (4). In the acidic environment of the stomach, hexavalent chromium can be readily reduced to trivalent chromium by reducing substances present in food, which limits the ingestion of hexavalent chromium (5-7).

Function

Trivalent chromium has been proposed to be the cofactor for a biologically active molecule that could enhance the effects of insulin on target tissues. Insulin is secreted by specialized cells in the pancreas in response to increased blood glucose concentration, such as after a meal. Insulin binds to insulin receptors on the surface of cells, activating the receptors and stimulating glucose uptake by cells. Through its interaction with insulin receptors, insulin provides cells with glucose for energy and helps maintain blood glucose within a narrow range of concentrations. In addition to its effects on carbohydrate (glucose) metabolism, insulin also influences the metabolism of fat and protein (8). Together, a decreased response to insulin or decreased insulin sensitivity in peripheral tissues (adipose tissue, muscle, and liver) and a progressive defect in insulin secretion may result in impaired glucose tolerance, frequently leading to overt type 2 diabetes mellitus. The body initially increases the secretion of insulin by specialized pancreatic cells to overcome the decrease in insulin sensitivity. However, the pancreas eventually fails to produce enough insulin to maintain normal blood glucose concentrations. Individuals with type 2 diabetes are at increased risk for cardiovascular disease (9).

Possible mechanism of action

The precise composition and structure of the biologically active form of chromium is not known. One model postulates that trivalent chromium might be the cofactor of a low-molecular-weight chromium-binding substance known as LMWCr or chromodulin (10). Chromodulin has been shown to play a role in the transport of chromium from the tissues to the bloodstream for ultimate elimination in the urine (11). When chromium is consumed at high levels, such as from dietary supplements, levels of chromodulin in tissues rise. At these high levels, chromodulin is proposed to enhance the cascade of signaling events induced by the binding of insulin to extracellular α-subunit of the insulin receptor (IR) (12). Upon insulin binding, the tyrosine kinase domain of the intracellular β-subunit of the IR becomes activated and causes the phosphorylation of tyrosine residues in the β-subunit itself. Subsequently, IR activation triggers a series of rapid phosphorylation reactions that activate many downstream effectors, eventually resulting in an increase in glucose uptake and storage (10). While this model is supported by *in vitro* studies, this mode of action for chromodulin has not been confirmed to date by *in vivo* studies.

Some, but not all, studies conducted in cell-based and animal models of insulin resistance and diabetes mellitus have found that chromium inhibits the activity of protein tyrosine phosphatase-1B (PTP-1B) and other negative regulators of insulin signaling, suggesting that chromium might improve insulin sensitivity under insulin-resistant conditions (reviewed in 10). A study in diabetic mice also suggested that chromium may reduce insulin clearance and enhance insulin signaling by inhibiting the proteolysis (degradation) of insulin and some downstream effectors (13). Additional mechanisms that may underlie the effect of chromium on insulin sensitivity, such as the reduction of markers of oxidative stress and inflammation known to contribute to insulin resistance, are under investigation (reviewed in 10, 14).

Nutrient interactions

Iron

Chromium competes for one of the binding sites on the iron transport protein, transferrin. However, supplementation of older men with 925 μg/day of chromium for 12 weeks did not significantly affect measures of iron nutritional status (15). A study of younger men found an insignificant decrease in transferrin saturation with iron after supplementation of 200 μg/day of chromium for eight weeks, but no long-term studies have addressed this issue (16). In a 12-week, randomized controlled trial, supplementation with chromium picolinate (200 μg/day) did not affect iron nutritional status in premenopausal women when compared to picolinic acid or placebo (17). Iron overload in hereditary hemochromatosis may interfere with chromium transport by competing for transferrin binding. It has been hypothesized that decreased chromium transport might contribute to the pathogenesis of diabetes mellitus in patients with hereditary hemochromatosis (5).

Vitamin C

Chromium uptake is enhanced in animals when given at the same time as vitamin C (7). In a study of three women, administration of 100 mg of vitamin C together with 1 mg of chromium resulted in higher plasma levels of chromium than 1 mg of chromium without vitamin C (5).

Carbohydrates

Compared to diets rich in complex carbohydrates (e.g., whole grains), diets high in simple sugars (e.g., sucrose) result in increased urinary chromium excretion in adults. This effect may be related to increased insulin secretion in response to the consumption of simple sugars compared to complex carbohydrates (5).

Deficiency

Dietary chromium deficiency has not been observed in humans. Potential cases of chromium deficiency were thought to have been observed in a few patients on long-term intravenous feeding (parenteral nutrition) who did not receive supplemental chromium in their intravenous solutions. The subjects developed abnormal glucose utilization and increased insulin requirements that responded to chromium supplementation (18). However, because intravenous solutions provide chromium at doses well above dietary levels, it has been suggested that chromium might produce biological effects only at pharmacological doses (3, 14). However, the differences in symptoms among subjects, the range of doses of chromium utilized over varying windows of time, and the different reported outcomes are now realized to make interpretation of these results difficult, even in terms of any potential pharmacological effects from the chromium supplementation. Because chromium appeared to enhance the action of insulin and chromium deficiency has been proposed to result in impaired glucose tolerance, chromium insufficiency has been hypothesized to be a contributing factor to the development of type 2 diabetes mellitus (5, 19). However, evidence for this is ambiguous at best.

Urinary chromium loss was reportedly increased by endurance exercise in male runners, suggesting that chromium needs may be greater in individuals who exercise regularly (20). In one study, weightlifting (resistive exercise) was found to increase urinary excretion of chromium in older men. However, chromium absorption also increased, leading to little or no net loss of chromium as a result of resistive exercise (21).

The absence of animal models for chromium deficiency makes it difficult to study possible biochemical, physiological, and functional abnormalities associated with inadequate intakes of chromium (if chromium is nutritionally essential) (2).

The Adequate Intake (AI)

Because there was not enough information to set an estimated average requirement (EAR), the Food and Nutrition Board (FNB) of the US Institute of Medicine (now the National Academy of Medicine) established an adequate intake (AI) based on the chromium content in healthy diets (**Table 1**; 5).

Table 1. Adequate Intake (AI) for Chromium

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	0.2	0.2
Infants	7-12 months	5.5	5.5
Children	1-3 years	11	11
Children	4-8 years	15	15
Children	9-13 years	25	21
Adolescents	14-18 years	35	24
Adults	19-50 years	35	25
Adults	51 years and older	30	20
Pregnancy	18 years and younger	-	29

Pregnancy	19 years and older	-	30
Breast-feeding	18 years and younger	-	44
Breast-feeding	19 years and older	-	45

The case of trivalent chromium essentiality has been questioned in both animals and humans in the last decades, and in 2014 the European Food Safety Authority's Panel on Dietetic Products, Nutrition, and Allergies — which provides dietary guidelines for the EU community — concluded that requirements for chromium could not be established (2). The FNB, which sets dietary intake recommendations for the United States and Canada, is not currently reconsidering the AI level for chromium (22).

Disease Prevention

Impaired glucose tolerance and type 2 diabetes mellitus

Early controlled studies in subjects with impaired glucose tolerance reported that chromium supplementation improved some measure of glucose utilization or had beneficial effects on blood lipid profiles (23). Impaired glucose tolerance refers to a prediabetic state and is currently defined by the presence of impaired fasting glucose (fasting plasma glucose concentration of 100-125 mg/dL) and impaired glucose tolerance status (plasma glucose concentration of 140-199 mg/dL during a two-hour challenge test with a 75-g oral glucose load) (24). Impaired glucose tolerance is associated with modest increases in risk of cardiovascular disease, as well as other traditional microvascular complications of diabetes mellitus (25). Current estimates suggest that up to 70% of individuals with impaired glucose tolerance eventually develop type 2 diabetes (26).

In a randomized, double-blind, placebo-controlled study in 56 subjects at risk of developing type 2 diabetes, six months of daily chromium picolinate supplementation (500 μg or 1,000 μg) had no effect on glucose and insulin concentrations, insulin sensitivity, and blood lipid profiles (27). Another randomized, placebo-controlled trial in 31 individuals without diabetes reported a great variability in serum and urinary chromium concentrations in response to a daily supplementation with 1,000 μg of chromium picolinate for 16 weeks. Also, in the chromium-supplemented group, participants with higher *vs.* lower serum chromium concentrations (>3.1 μg/L *vs.* ≤3.1 μg/L) exhibited a decline in insulin sensitivity that could not be explained by expression changes in the genes involved in insulin signaling (28). Additionally, a meta-analysis of nine randomized clinical trials published between 1992 and 2010 reported that chromium at doses of 200-1,000 μg/day for 8-16 weeks had no effect on fasting glucose concentrations in 309 individuals without diabetes (29).

Cardiovascular disease

Impaired glucose tolerance and type 2 diabetes mellitus are associated with adverse changes in lipid profiles and increased risk of cardiovascular disease. Studies examining the effects of chromium supplementation on lipid profiles have given inconsistent results. While some studies have observed reductions in serum total cholesterol, LDL-cholesterol, and triglyceride levels or increases in HDL-cholesterol levels, others have observed no effect. Such mixed responses of lipid and lipoprotein levels to chromium supplementation may reflect differences in chromium nutritional status. It is possible that only individuals with insufficient dietary intake of chromium will experience beneficial effects on lipid profiles after chromium supplementation (6, 7, 30).

Moreover, a recent meta-analysis of 10 randomized controlled trials, mostly in patients with type 2 diabetes mellitus or metabolic syndrome, found chromium supplementation had no effect on either systolic or diastolic blood pressure (31). Yet, another meta-analysis of randomized controlled trials found chromium supplementation decreased circulating levels of two proinflammatory biomarkers associated with increased cardiovascular risk, hs-CRP and TNF-α, but not blood levels of IL-6 (32).

Health claims

Increases muscle mass

Claims that chromium supplementation increases lean body mass and decreases body fat are based on the relationship between chromium and insulin action (see Function). In addition to regulating glucose metabolism, insulin is known to affect fat and protein metabolism (8). At least 12 placebo-controlled studies have compared the effect of chromium supplementation (172-1,000 μg/day of chromium as chromium picolinate) with or without an exercise program on lean body mass and measures of body fat (reviewed in 33). In general, the studies that used the most sensitive and accurate methods of measuring body fat and lean mass (dual energy x-ray absorbtiometry or DEXA and hydrodensitometry or underwater weighing) did not find a beneficial effect of chromium supplementation on body composition (6, 30). In the US, the claim that chromium picolinate increases lean body mass is not allowed on supplement labels because it is not substantiated by the available research (34, 35).

Promotes weight loss

Controlled studies of chromium supplementation have demonstrated little if any beneficial effect on weight or fat loss, and claims of weight loss in humans appear to be exaggerated. In 1996, the US Federal Trade Commission (FTC) ruled that there was no scientific basis for claims that chromium picolinate could promote weight loss and fat loss in humans (36). A 2013 meta-analysis of 11 randomized, double-blind, placebo-controlled trials in 866 overweight or obese subjects found a significant 0.50-kilogram (1.10-pound) reduction in body weight with supplemental chromium (most exclusively in the form of chromium picolinate) at doses between 137 μg/day and 1,000 μg/day for 8 to 24 weeks (37). However, such a small change did not reach a clinically significant weight loss of ≥5% of the initial body weight (38). A 2019 meta-analysis of 19 clinical trials found similar results: chromium supplementation at doses between 20 μg/day and 1,000 μg/day for 4 to 24 weeks decreased body weight in overweight or obese subjects by only 0.75 kg, a clinically insignificant amount (39). Some reports have suggested that supplemental chromium may reduce food craving and intake in overweight or obese women (40, 41). Yet, current available data remain insufficient to support the use of chromium supplements as a weight-loss strategy (42). In the US, the claim that chromium picolinate promotes weight loss is not allowed on supplement labels because it is unsubstantiated (34, 35).

Reduces insulin resistance

Despite stating that scientific evidence is severely limited, the US FDA allows a single claim on supplement labels: "One small study suggests that chromium picolinate may reduce the risk of insulin resistance, and therefore possibly may reduce the risk of type 2 diabetes. FDA concludes, however, that the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes is highly uncertain." (35, 43).

Disease Treatment

Type 2 diabetes mellitus

Type 2 diabetes mellitus is characterized by chronic hyperglycemia (elevated blood glucose concentration) and insulin resistance. Because resistance to insulin is usually associated with a compensatory rise in insulin secretion, circulating insulin concentrations in people with type 2 diabetes may be higher than in healthy individuals. Yet, the resistance of peripheral tissues (especially liver and skeletal muscle) to insulin also implies that the physiological effects of insulin are reduced.

Since cell culture and rodent models of diabetes have implicated chromium in the regulation of insulin sensitivity and blood glucose levels, the relationship between chromium nutritional status and type 2 diabetes mellitus has generated considerable scientific interest. Early reports observed that individuals with overt type 2 diabetes for over two years had higher rates of urinary chromium loss than healthy individuals (44). Small, well-designed studies of chromium supplementation in individuals with type 2 diabetes showed no improvement in blood glucose control, although they provided some evidence of reduced insulin concentrations and improved blood lipid profiles (45). In 1997, the results of a placebo-controlled trial conducted in China indicated that chromium supplementation might be beneficial in the treatment of type 2 diabetes (46). One hundred and eighty participants were randomized to receive either a placebo or chromium supplements in the form of chromium picolinate at either 200 μg/day or 1,000 μg/day. After four months of treatment, fasting blood glucose concentrations were found to be 15% to 19% lower in those who took 1,000 μg/day of chromium compared to those who took the placebo. Yet, blood glucose concentrations in those taking 200 μg/day of chromium did not differ significantly from those who took placebo. Chromium picolinate at either 200 μg/day or 1,000 μg/day was also associated with reduced insulin concentrations compared to placebo. The level of glycated hemoglobin A1c (HbA1c), a measure of glycemic control over the past four months, was also significantly reduced in both chromium-supplemented groups. However, a number of limitations made it difficult to extrapolate the results to the US population (47). Besides, the study was excluded from meta-analyses of randomized controlled trials due to insufficient data quality (29, 48).

In a recent systematic review and meta-analysis of randomized controlled trials in patients with type 2 diabetes, chromium supplementation (50-1,000 μg/day for 4 to 25 weeks) reduced concentrations of fasting plasma glucose (23 trials) and insulin (14 trials), and improved HbA1c values (18 trials) (49). These effects were not dose dependent (49). Yet, other meta-analyses in patients with type 2 diabetes did not find significant benefits of chromium supplementation on fasting glucose and insulin (50) or HbA1C (51). Moreover, a systematic review on 20 randomized controlled trials found that only a handful of chromium supplementation studies resulted in glycemic changes that are considered clinically meaningful, i.e., consistent with treatment goals of a 7.2-mmol/dL decrease in fasting glucose, a decrease of 0.5% in HbA1c, or reaching ≤7% HbA1c (52).

Gestational diabetes

Few studies have examined the effects of chromium supplementation on gestational diabetes mellitus, a condition that is estimated to affect 5.8% to 9.2% of pregnant women in the US (53). The occurrence of gestational diabetes during pregnancy is associated with insufficient insulin secretion and glucose intolerance of variable severity (54). Peripheral insulin resistance usually increases in the second or third trimester of pregnancy. Because elevated maternal blood glucose concentrations can have adverse effects on the developing fetus, women with gestational diabetes are at increased risk of pregnancy complications (55). After delivery, impaired glucose tolerance generally reverts to normal glucose tolerance. However, nearly one-third of women who have had gestational diabetes develop postpartum glucose intolerance (prediabetes or type 2 diabetes) (56, 57). The question also arises as to whether low chromium levels might be an effect rather than a contributing factor in gestational diabetes.

An observational study in pregnant women did not find serum chromium levels to be associated with measures of glucose tolerance or insulin resistance in late pregnancy (58). However, it is not known whether measures of serum chromium levels truly reflect tissue chromium levels and chromium status during pregnancy. A more recent prospective study following 425 pregnant women also failed to find a correlation between serum chromium concentrations and incidence of gestational diabetes (59). A cross-sectional study of 90 pregnant women in southern India found that those with gestational diabetes had significantly lower serum chromium concentrations compared to gestational diabetes-free women. Given the above mixed results, it should be noted that different methods were used to measure circulating chromium concentrations in each study. Also, it is possible that nutritional chromium status may vary among ethnically distinct populations so that studies including pregnant women from different ethnic backgrounds and/or geographical areas would give different results.

In addition, there is currently insufficient evidence to evaluate the effect of supplemental chromium on gestational diabetes. Women with gestational diabetes whose diets were supplemented with 4 μg of chromium per kilogram of body weight daily as chromium picolinate for eight weeks had decreased fasting blood glucose and insulin concentrations compared to those who took a placebo. Yet, insulin therapy rather than chromium picolinate was required to normalize severely elevated blood glucose levels (6, 60).

Metabolic syndrome

Metabolic syndrome is a combination of medical conditions, including hypertension, dyslipidemia, central obesity, and insulin resistance, that places one at increased risk for cardiovascular disease and type 2 diabetes mellitus (see the page: Metabolic Syndrome). A prospective cohort study that followed 3,648 young US adults for 23 years found an inverse association between toenail chromium concentration measured at baseline and risk of developing metabolic syndrome (61). An inverse association between plasma chromium concentration and metabolic syndrome was also observed in a case-control study in 4,282 Chinese adults (62). However, low toenail and plasma chromium may be the result of metabolic syndrome, rather than suggesting a cause or contributing factor.

Only a few randomized controlled trials have examined whether chromium supplementation might benefit patients with metabolic syndrome. In a randomized, double-blind, placebo-controlled trial in 65 patients with metabolic syndrome, 300 μg/day of supplemental chromium (from chromium-enriched yeast) for 24 weeks had no effect on measured parameters of glucose, insulin, and lipid metabolism (63). While large-scale trials would be needed, there is presently no evidence that chromium can help treat metabolic syndrome.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of childbearing age, with an estimated worldwide prevalence of 21% (64). The disorder has a multifactorial etiology and is characterized by menstrual irregularities, polycystic ovaries, and infertility. Similar to metabolic syndrome, women with PCOS often have various metabolic abnormalities, including dyslipidemia, obesity (especially abdominal obesity), impaired glucose tolerance, insulin resistance, and are at increased risk for developing type 2 diabetes mellitus (65).

Several randomized controlled trials have evaluated whether chromium supplementation might help treat PCOS, but the results are conflicting. A 2017 systematic review and meta-analysis of seven clinical trials found that chromium picolinate supplementation (of either 200 μg/day or 1,000 ug/day) for 8 to 24 weeks decreased BMI (3 studies), lowered free testosterone concentration (5 studies), and decreased fasting serum insulin concentration (5 studies) but had no effect on concentrations of fasting blood glucose (4 studies), total testosterone (3 studies), luteinizing hormone (3 studies), or follicle-stimulating hormone (2 studies) (66). However, other recent systematic reviews and meta-analyses have concluded that chromium supplementation in women with PCOS does not result in significant or clinically meaningful health benefits, including with respect to glucose and insulin metabolism (67-69).

Sources

Food sources

The amount of chromium in food is variable and has been measured accurately in relatively few foods. Presently, there is no large database for the chromium content of food. Whole-grain products, high-bran cereals, green beans, broccoli, nuts, and egg yolk are good sources of chromium. Processed meats may also be high in chromium, depending on the processing equipment and method (70). Foods high in simple sugars, such as sucrose and fructose, are usually low in chromium and may actually promote chromium excretion (6, 71). Estimated average chromium intakes in the US range from 23 μg/day-29 μg/day for adult women and 39-54 μg/day for adult men (5). The chromium content of some foods is listed in **Table 2** and expressed in micrograms (μg) (72). Since chromium content varies significantly between different batches of the same food, the information provided in the table should serve only as a guide to the chromium content of food.

Table 2. Some Food Sources of Chromium

Food	Serving	Chromium (μg)
Broccoli	½ cup	11.0
Green beans	½ cup	1.1
Potatoes (mashed)	1 cup	2.7
Grape juice	8 fl. ounces	7.5
Orange juice	8 fl. ounces	2.2
Beef	3 ounces	2.0
Turkey breast	3 ounces	1.7
Turkey ham (processed)	3 ounces	10.4
Waffle	1 (~2.5 ounces)	6.7
Bagel	1	2.5
English muffin	1	3.6
Apple w/ peel	1 medium	1.4
Banana	1 medium	1.0

Supplements

Trivalent chromium is available as a supplement in several forms, including chromium chloride, chromium nicotinate, chromium picolinate, and high-chromium yeast. These are available as stand-alone supplements or in combination products, including multivitamin/mineral supplements. Doses typically range from 100 to 300 μg of elemental chromium in single-nutrient supplements and from 10 to 180 μg in multivitamin/mineral supplements (73).

Much of the research on impaired glucose tolerance and type 2 diabetes mellitus uses chromium picolinate as the source of chromium, although investigations suggest that its bioavailability may not be greater than that of dietary chromium (74). Some concerns have been raised over the long-term safety of chromium picolinate supplementation (see Safety).

Safety

Toxicity

Hexavalent chromium (chromium VI; Cr^{6+}) is a recognized carcinogen, with inhalation causing lung, nasal, and sinus cancers (75). Exposure to hexavalent chromium in dust has been associated with an increased incidence of lung cancer and is known to cause inflammation of the skin (dermatitis).

In contrast, there is little evidence that trivalent chromium (chromium III; Cr3+) is toxic to humans. The toxicity from oral intakes is considered to be low because ingested chromium is poorly absorbed, and most absorbed chromium is rapidly excreted in the urine (76). Because no adverse effects have been convincingly associated with excess intake of trivalent chromium from food or supplements, the Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) did not set a tolerable upper intake level (UL) for chromium. Yet, despite limited evidence for adverse effects, the FNB acknowledged the possibility of a negative impact of high oral intakes of supplemental trivalent chromium on health and advised caution (5).

Chromium picolinate

Most of the concerns regarding the long-term safety of trivalent chromium supplementation arise from several studies in cell culture, suggesting trivalent chromium, especially in the form of chromium picolinate, may increase DNA damage (77-80). A study in 10 women taking 400 μg/day of chromium as chromium picolinate found no evidence of increased oxidative damage to DNA as measured by antibodies to an oxidized DNA base (81).

Many studies have demonstrated the safety of daily doses of up to 1,000 μg of chromium for several months (46, 82). However, there have been a few isolated reports of serious adverse reactions to chromium picolinate. Kidney failure was reported five months after a six-week course of 600 μg/day of chromium in the form of chromium picolinate (83), while kidney failure and impaired liver function were reported after the use of 1,200 to 2,400 μg/day of chromium in the form of chromium picolinate over a period of four to five months (84). Additionally, a 24-year old healthy male reportedly developed reversible, acute renal failure after taking chromium picolinate-containing supplements for two weeks (85). Individuals with pre-existing kidney or liver disease may be at increased risk of adverse effects and should limit supplemental chromium intake (5).

Drug interactions

Little is known about drug interactions with chromium in humans. Large doses of calcium carbonate or magnesium hydroxide-containing antacids decreased chromium absorption in rats. In contrast, non-steroidal anti-inflammatory drugs, aspirin and indomethacin, can increase chromium absorption in rats (7).

Linus Pauling Institute Recommendation

The lack of any known indicators of chromium nutritional status in humans makes it difficult to determine the level of chromium intake most likely to promote optimum health, if such exists. Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement containing 100% of the daily values (DV) of most nutrients may provide 10 to 180 μg/day of chromium, which is generally considered safe.

Older adults (>50 years)

Although the requirement for chromium is not known to be higher for older adults, one study found that chromium concentrations in hair, sweat, and urine decreased with age (86). Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement containing 100% of the daily values (DV) of most nutrients should provide sufficient chromium for older adults.

Because impaired glucose tolerance, type 2 diabetes mellitus, and metabolic syndrome are associated with serious health problems, individuals with any of these conditions should seek medical advice if considering the use of high-dose chromium supplements.

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Copper

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Español

Summary

- Copper is an essential cofactor for oxidation-reduction reactions involving copper-containing oxidases. Copper enzymes regulate various physiologic pathways, such as energy production, iron metabolism, connective tissue maturation, and neurotransmission. *(More information)*
- Copper deficiency can result from malnutrition, malabsorption, or excessive zinc intake and can be acquired or inherited. Symptoms include deficiencies in blood cells, bone and connective tissue abnormalities, and neurologic disorders. *(More information)*
- Marginal copper imbalance has been linked to impaired immune function, bone demineralization, and increased risk of cardiovascular and neurodegenerative diseases. However, the use of more precise indicators of nutritional copper status needs to be considered for future research. *(More information)*
- Organ meats, shellfish, nuts, seeds, wheat-bran cereals, and whole-grain products are good sources of copper. *(More information)*
- Copper toxicity is rare and often associated with genetic defects of copper metabolism. *(More information)*

Copper (Cu) is an essential trace element for humans and animals. In the body, copper shifts between the cuprous (Cu^{1+}) and cupric (Cu^{2+}) forms, though the majority of the body's copper is in the Cu^{2+} form. The ability of copper to easily accept and donate electrons explains its important role in oxidation-reduction (redox) reactions and in scavenging free radicals (1). Although Hippocrates is said to have prescribed copper compounds to treat diseases as early as 400 B.C. (2), scientists are still uncovering new information regarding the functions of copper in the human body (3).

Function

Copper is a critical functional component of several essential enzymes known as cuproenzymes (4). Some of the physiologic functions known to be copper-dependent are discussed below.

Energy production

The copper-dependent enzyme, cytochrome *c* oxidase, plays a critical role in cellular energy production. By catalyzing the reduction of molecular oxygen (O_2) to water (H_2O), cytochrome *c* oxidase generates an electrical gradient used by the mitochondria to create the vital energy-storing molecule, ATP (5).

Connective tissue formation

Another cuproenzyme, lysyl oxidase, is required for the cross-linking of collagen and elastin, which are essential for the formation of strong and flexible connective tissue. The action of lysyl oxidase helps maintain the integrity of connective tissue in the heart and blood vessels and also plays a role in bone formation (2).

Iron metabolism

Four copper-containing enzymes, known as multi-copper oxidases (MCO) or ferroxidases, have the capacity to oxidize ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), the form of iron that can be loaded onto the protein transferrin for transport to the site of red blood cell formation. The MCO family comprises the circulating ceruloplasmin (which represents ~90% of plasma copper), the membrane-bound ceruloplasmin (called GPI-ceruloplasmin), and two proteins called Hephaestin and Zyklopen found in the intestine and the placenta, respectively (6). Interestingly, mice that do not express ceruloplasmin ($Cp^{-/-}$) have normal copper metabolism but abnormal iron accumulation in the liver (7, 8). Similarly, individuals lacking ceruloplasmin display iron overload in selected tissues, including liver, brain, and retina (9). This supports the idea that the ferroxidase activity of ceruloplasmin is essential to the flux of iron in the body. Moreover, the fact that iron mobilization from storage sites is impaired in copper deficiency supports the role of MCO in iron metabolism (10).

Central nervous system

A number of reactions essential to normal function of the brain and nervous system are catalyzed by cuproenzymes.

Neurotransmitter synthesis

Dopamine β-hydroxylase catalyzes the conversion of dopamine to the neurotransmitter, norepinephrine (11).

Formation and maintenance of myelin

The myelin sheath is made of phospholipids whose synthesis depends on cytochrome *c* oxidase activity (2).

Melanin formation

The cuproenzyme, tyrosinase, is required for the formation of the pigment melanin. Melanin is formed in cells called melanocytes and plays a role in the pigmentation of the hair, skin, and eyes (2).

Antioxidant functions

Superoxide dismutase

Superoxide dismutase (SOD) functions as an antioxidant by catalyzing the conversion of superoxide radicals (free radicals or ROS) to hydrogen peroxide, which can subsequently be reduced to water by other antioxidant enzymes (12). Two forms of SOD contain copper: (1) copper/zinc SOD is found within most cells of the body, including red blood cells; and (2) extracellular SOD is a copper-containing enzyme found at high levels in the lungs and low levels in plasma (2).

Ceruloplasmin

Ceruloplasmin may function as an antioxidant in two different ways. Free copper and iron ions are powerful catalysts of free-radical damage. By binding copper, ceruloplasmin prevents free copper ions from catalyzing oxidative damage. The ferroxidase activity of ceruloplasmin (oxidation of ferrous iron) facilitates iron loading onto its transport protein, transferrin, and may prevent free ferrous ions (Fe^{2+}) from participating in harmful free-radical-generating reactions (12).

Regulation of gene expression

Cellular copper levels may affect the synthesis of proteins by enhancing or inhibiting the transcription of specific genes. Copper may regulate the expression of genes by increasing the level of intracellular oxidative stress. A number of signal transduction pathways are activated in response to oxidative stress and can lead to an increase in the expression of genes involved in the detoxification of reactive oxygen species (13).

Nutrient interactions

Iron

Adequate copper nutritional status is necessary for normal iron metabolism and red blood cell formation. Anemia is a clinical sign of copper deficiency, and iron has been found to accumulate in the livers of copper-deficient animals, indicating that copper (via the copper-containing ceruloplasmin) is required for iron transport to the bone marrow for red blood cell formation (see Iron metabolism) (2). The connection between copper availability and iron metabolism has also been established in humans; copper deficiency can lead to secondary ceruloplasmin deficiency and hepatic iron overload and/or cirrhosis (10). Oral copper supplementation restored normal ceruloplasmin levels and plasma ferroxidase activity and corrected the iron-metabolism disorder in a copper-deficient subject (14). Moreover, infants fed a high iron formula absorbed less copper than infants fed a low iron formula, suggesting that high iron intakes may interfere with copper absorption in infants (15).

Zinc

High supplemental zinc intakes of 50 mg/day or more for extended periods of time may result in copper deficiency. High dietary zinc intakes increase the synthesis of an intestinal cell protein called metallothionein, which binds certain metals and prevents their absorption by trapping them in intestinal cells. Metallothionein has a stronger affinity for copper than zinc, so high levels of metallothionein induced by excess zinc cause a decrease in copper absorption. In contrast, high copper intakes have not been found to affect zinc nutritional status (2, 15). Zinc supplementation (10 mg/day for eight weeks) was able to restore normal plasma copper/zinc ratios in 65 subjects on long-term hemodialysis who initially exhibited low zinc levels and elevated copper levels. Whether improving zinc and copper status of hemodialysis patients can impact their clinical outcomes needs to be assessed (16).

Fructose

High fructose diets have exacerbated copper deficiency in rats but not in pigs whose gastrointestinal systems are more like those of humans. Very high levels of dietary fructose (20% of total calories) did not result in copper depletion in humans, suggesting that fructose intake does not result in copper depletion at levels relevant to normal diets (2, 15).

Vitamin C

Although vitamin C supplements have produced copper deficiency in guinea pigs (17), the effect of vitamin C supplements on copper nutritional status in humans is less clear. Two small studies in healthy, young adult men indicate that the oxidase activity of ceruloplasmin may be impaired by relatively high doses of supplemental vitamin C. In one study, vitamin C supplementation of 1,500 mg/day for two months resulted in a significant decline in ceruloplasmin oxidase activity (18). In the other study, supplements of 605 mg/day of vitamin C for three weeks resulted in decreased ceruloplasmin oxidase activity, although copper absorption did not decline (19). Neither of these studies found vitamin C supplementation to adversely affect copper nutritional status.

Deficiency

Clinically evident or frank dietary copper deficiency is relatively uncommon. Serum copper and ceruloplasmin levels may fall to 30% of normal in cases of severe copper deficiency. Hypocupremia (low copper content in blood) is also observed in genetic disorders of copper metabolism, such as aceruloplasminemia and, paradoxically, in Wilson's disease, which are not linked to dietary copper deficiency. One of the most common clinical signs of copper deficiency is an anemia that is unresponsive to iron therapy but corrected by copper supplementation. Although the anemia is thought to result from defective iron mobilization due to decreased ceruloplasmin activity, the absence of ceruloplasmin in individuals with inherited aceruloplasminemia is not always associated with overt anemia (20). Copper deficiency may also lead to abnormally low numbers of white blood cells known as neutrophils (neutropenia), a condition that may be accompanied by increased susceptibility to infection. Copper depletion studies have suggested that reduced copper availability might affect erythroid and myeloid cell lineage, supporting a role for copper in the regulation of blood cell renewal (21, 22). More research is clearly needed to uncover the mechanisms underlying copper deficiency-induced anemia and neutropenia (4, 23). Osteoporosis and other abnormalities of bone development related to copper deficiency are most common in copper-deficient, low-birth-weight infants and young children. Less common features of copper deficiency may include loss of pigmentation, neurological symptoms, and impaired growth (2, 5).

Individuals at risk of deficiency

Cow's milk is relatively low in copper, and cases of copper deficiency have been reported in high-risk infants and children fed only cow's milk formula (24). High-risk individuals include premature infants (especially low-birth-weight infants); infants with prolonged diarrhea; infants and children recovering from malnutrition; and individuals with malabsorption syndromes, including celiac disease, sprue, and short bowel syndrome due to surgical removal of large portions of the intestine. Individuals receiving intravenous total parenteral nutrition lacking copper or other restricted diets may also require supplementation with copper and other trace elements (2, 5). Copper deficiency in infants with cholestasis (reduced biliary excretion of copper) has been linked to long-term parenteral nutrition lacking copper (25). Case reports indicate that cystic fibrosis patients may also be at increased risk of copper insufficiency (26). Finally, excessive zinc intake has led to secondary copper deficiency in individuals using zinc supplements or zinc-enriched dental creams (27, 28).

Acquired copper deficiency

A neurologic syndrome has been described in adults with acquired copper deficiency (29). The symptoms include central nervous system demyelination, polyneuropathy, myelopathy, and inflammation of the optic nerve. The etiology is unknown in absence of prominent risk factors (see Individuals at risk of deficiency); case reports describe increased intestinal copper content suggesting a malabsorption syndrome like Menkes disease, but mutations in *ATP7A* gene were not linked to the condition (30) (see Inherited copper deficiency). Oral copper replacement (2 mg/day of elemental copper) normalizes serum copper and ceruloplasmin concentrations, stabilizes the condition, and significantly improves the quality of life of affected subjects. However, the duration of copper supplementation has not yet been established, and dosing increments might be required in cases of relapse (29).

Inherited copper deficiency

Copper trafficking within most cells except hepatocytes (liver cells) is facilitated by a Cu^{1+}-transporting ATPase called ATP7A. Mutations in the *ATP7A* gene impair the transport of intracellular copper, which accumulates in the cytosol of enterocytes and vascular endothelial cells (31). This results in systemic copper deficiency and decreased cuproenzyme activity. Copper transport into the brain is also affected, leading to copper accumulation in the blood-brain barrier and reduced cuproenzyme activity in neurons. Affected individuals are diagnosed with Menkes disease (MD) or with a milder form of the disease called occipital horn syndrome (OHS). The clinical features of MD include intractable seizures, connective tissue disorders, subdural hemorrhage, and hair abnormalities ("kinky hair"). OHS patients exhibit muscular hypotonia and connective tissue abnormalities, including exostosis on occipital bones. Subcutaneous injections of copper-histidine are used to bypass the defective intestinal absorption and improve copper metabolic function in patients. However, copper entry into the brain remains limited (reviewed in 32).

The Recommended Dietary Allowance (RDA)

A variety of indicators were used to establish the RDA for copper, including plasma copper concentration, serum ceruloplasmin activity, superoxide dismutase activity in red blood cells, and platelet copper concentration (15). The RDA for copper reflects the results of depletion-repletion studies and is based on the prevention of deficiency (**Table 1**).

Table 1. Recommended Dietary Allowance (RDA) for Copper

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	200 (AI)	200 (AI)
Infants	7-12 months	220 (AI)	220 (AI)
Children	1-3 years	340	340
Children	4-8 years	440	440
Children	9-13 years	700	700
Adolescents	14-18 years	890	890
Adults	19 years and older	900	900
Pregnancy	all ages	-	1,000
Breast-feeding	all ages	-	1,300

Disease Prevention

Cardiovascular disease

While it is clear that severe copper deficiency results in heart abnormalities and damage (cardiomyopathy) in some animal species, the pathology differs from atherosclerotic cardiovascular disease that is prevalent in humans (15). Studies in humans have produced inconsistent results, and their interpretation is hindered by the lack of a reliable marker of copper nutritional status. Outside the body, free copper is known to be a pro-oxidant and is frequently used to produce oxidation of low-density lipoprotein (LDL) in the test tube. The copper-containing protein ceruloplasmin has been found to stimulate LDL oxidation in the test tube (33), leading some scientists to propose that increased copper levels could increase the risk of atherosclerosis by promoting the oxidation of LDL. However, there is little evidence that copper or ceruloplasmin promotes LDL oxidation in the human body. Additionally, the cuproenzymes, superoxide dismutase and ceruloplasmin, are known to have antioxidant properties, leading some experts to propose that copper deficiency rather than excess copper increases the risk of cardiovascular disease (34).

Epidemiological studies

Several epidemiological studies have found increased serum copper levels to be associated with increased risk of cardiovascular disease. A prospective cohort study in the US examined serum copper levels in more than 4,500 men and women 30 years of age and older (35). During the following 16 years, 151 participants died from coronary heart disease (CHD). After adjusting for other risk factors of heart disease, those with serum copper levels in the two highest quartiles had a significantly greater risk of dying from CHD. Three other case-control studies conducted in Europe had similar findings. One small study in 60 patients with chronic heart failure or ischemic heart disease reported that serum copper was a predictor of short-term outcome (36). Another prospective cohort study in 4,035 middle-aged men reported that high serum copper levels were significantly related to a 50% increase in all-cause mortality; however, serum copper was not significantly associated with cardiovascular mortality in this study (37). Additionally, serum copper has been found to be elevated in patients with rheumatic heart disease (38).

It is important to note that serum copper largely reflects serum ceruloplasmin and is not a sensitive indicator of copper nutritional status (39). Serum ceruloplasmin levels are known to increase by 50% or more under certain conditions of physical stress, such as trauma, inflammation, or disease. Because over 90% of serum copper is carried in ceruloplasmin, which is increased in many inflammatory conditions, elevated serum copper may simply be a marker of inflammation that accompanies atherosclerosis. In contrast to the epidemiological findings linking increased serum copper levels to heart disease, two autopsy studies found copper levels in heart muscle were actually lower in patients who died of CHD than those who died of other causes (40). Additionally, the copper content of white blood cells has been positively correlated with the degree of patency of coronary arteries in CHD patients (41, 42). Further, patients with a history of myocardial infarction (MI) had lower concentrations of extracellular superoxide dismutase (SOD) than those without a history of MI (43). Thus, due to a lack of a reliable biomarker of copper nutritional status, it is not clear whether copper is related to cardiovascular disease.

Intervention studies

While studies in very small numbers of adults fed experimental diets low in copper have demonstrated adverse changes in blood cholesterol levels, including increased total and LDL-cholesterol levels and decreased HDL-cholesterol levels (44), other studies have not confirmed those results (45). Copper supplementation of 2-3 mg/day for four to eight weeks did not result in clinically significant changes in cholesterol levels (34, 46, 47). Further, research has failed to find evidence that increased copper intake increases oxidative stress. In a multi-center, placebo-controlled trial, copper supplementation of 3 or 6 mg/day for six weeks did not result in increased susceptibility of LDL to oxidation induced outside the body (*ex vivo*) by copper or peroxynitrite (a reactive nitrogen species) (48). Moreover, supplementation with 3 or 6 mg/day of copper decreased the *in vitro* oxidizability of red blood cells (49), indicating that relatively high intakes of copper do not increase the susceptibility of LDL or red blood cells to oxidation.

Summary

Although free copper and ceruloplasmin can promote LDL oxidation in the test tube, there is little evidence that increased dietary copper increases oxidative stress in the human body. Increased serum copper levels have been associated with increased cardiovascular disease risk, but the significance of these findings is unclear due to the association between serum ceruloplasmin levels and inflammatory conditions. Clarification of the relationships between copper nutritional status, ceruloplasmin levels, and cardiovascular disease risk requires further research.

Notably, it was suggested that elevated plasma copper concentrations could be linked to high homocysteine levels in individuals with vascular diseases (50, 51). Increased levels of homocysteine are associated with arterial wall lesions and increased risk of cardiovascular disease (52). The interaction between homocysteine and copper was linked to impaired vascular endothelial function in animal models (53, 54). However, although copper restriction in animals has shown some beneficial effects on homocysteine levels and atherogenic lesions (55, 56), it is not known whether copper imbalance contributes to the atherogenic effect of homocysteine in humans.

Immune system function

Copper is known to play an important role in the development and maintenance of immune system function, but the exact mechanism of its action is not yet known. Neutropenia (abnormally low numbers of white blood cells called neutrophils) is a clinical sign of copper deficiency in humans. Adverse effects of insufficient copper on immune function appear most pronounced in infants. Infants with Menkes disease, a genetic disorder that results in severe copper deficiency, suffer from frequent and severe infections (57, 58). In a study of 11 malnourished infants with evidence of copper deficiency, the ability of certain white blood cells to engulf pathogens increased significantly after one month of copper supplementation (59). Moreover, 11 men on a low-copper diet (0.66 mg copper/day for 24 days and 0.38 mg/day for another 40 days) showed a decreased proliferation response when white blood cells, called monocytes, were isolated from their blood and presented with an immune challenge in cell culture (60). Recent mechanistic studies support a role for copper in innate immune response against bacterial infections (reviewed in 61). While severe copper deficiency has adverse effects on immune function, the effects of marginal copper insufficiency in humans are not yet clear.

Osteoporosis

The progressive loss of bone mineral density (BMD) leading to osteopenia (pre-osteoporosis) and osteoporosis is commonly observed in the elderly population. Women are more often affected by osteoporosis than men, (e.g., prevalence ratio is 5:1 in non-Hispanic whites) (62), primarily due to the postmenopausal reduction in estrogen production that is essential for maintaining strength of muscle, bone, and connective tissue (63). Osteoporosis is associated with an increased risk of falls, bone fracture, and mortality in individuals over 65 years of age (64). Osteoporosis has also been reported in infants with severe copper deficiency (65, 66), but it is not clear whether marginal copper deficiency during adulthood contributes to osteoporosis. While an increase in bone resorption (breakdown) was observed in 11 healthy adult males with a marginal copper intake of 0.7 mg/day for six weeks (67), the supplementation of 3 to 6 mg/day of copper for six weeks had no effect on biochemical markers of bone resorption or bone formation in two studies of healthy adult men and women (68, 69). However, it is possible that a reduction in copper intake and absorption in older people reduces the activity of the copper-dependent enzyme, lysyl oxidase, which is required for the maturation (cross-linking) of collagen—a key element in the organic matrix of bone.

Overall, research regarding the role of copper nutritional status in age-related osteoporosis is limited. An early study found that serum copper levels in 46 elderly patients with hip fractures were significantly lower than those of matched controls (70). However, another study found no differences in serum copper levels among postmenopausal women with normal BMD (N=40), osteopenia (N=40), or osteoporosis (N=40) (71). A small study in perimenopausal women, who consumed an average of 1 mg of dietary copper daily, reported decreased loss of BMD from the lumbar spine after copper supplementation of 3 mg/day for two years (72). Additionally, a two-year double-blind, placebo-controlled trial in 59 postmenopausal women found that a combination of supplemental calcium and trace minerals, including 2.5 mg of copper daily, resulted in maintenance of spinal bone density, whereas supplemental calcium or trace minerals, alone, were not effective in preventing loss of bone density (73). However, a more recent randomized, double-blind, placebo-controlled study, which initially enrolled 224 healthy, postmenopausal women aged 51 to 80 years, found daily supplementation with 600 mg of calcium, 2 mg of copper, and 12 mg of zinc for two years decreased whole-body BMD compared to supplemental calcium alone. Moreover, although BMD was clearly reduced in subjects with dietary copper intakes below the RDA (0.9 mg/day), supplemental copper did not prevent the progressive loss of BMD as well as the calcium regimen alone (74). Finally, several studies have suggested that tooth loss might be related to poor systemic BMD (75, 76). When compared with 20 healthy-matched controls, 50 patients (mean age 47.5 years) with low spinal BMD and advanced tooth wear were found with significantly lower copper content in tooth enamel. However, despite evidence suggesting bone demineralization, the serum copper levels in this population were similar to those of the healthy group (77). More research is required to draw conclusions regarding the effects of marginal copper deficiency and copper supplementation on bone metabolism and age-related osteoporosis.

Neurodegenerative diseases

Alzheimer's disease

Cognitive deterioration in individuals with Alzheimer's disease (AD) is linked to the presence of β-amyloid plaques and abnormal Tau protein-forming aggregates. The possibility that copper imbalance is involved in the onset of AD is currently investigated. First, it appears that the fraction of 'free' copper (not bound to ceruloplasmin) is augmented in copper homeostasis disorders, as well as in AD individuals (78, 79). Moreover, AD patients appear to have higher levels of serum copper compared to healthy controls (80). Among the many hypotheses supporting a role for copper in AD onset or progression, it is suggested that copper could be involved in the formation of senile plaques through hypermetallation of the β-amyloid peptides, possibly leading to zinc depletion, enhanced oxidative stress, and even brain damage (81, 82). Recent research has also identified genetic variations (polymorphisms) in the ATP7B gene that may modify the risk of developing AD (83). The protein, ATP7B, is responsible for the excretion of hepatic copper into the biliary tract, and its impairment in Wilson's disease results in increased 'free' copper level in blood and copper accumulation in liver and brain.

More research is needed to investigate whether genetic variants could influence the susceptibility of environmental exposure to high levels of copper. The addition of copper to drinking water has been associated with enhanced pathologic features in animal models of AD (84, 85). One study in a rabbit model reported that combining a high-cholesterol diet and copper (0.12 mg/L in drinking water) could impair cognition (84). A prospective cohort study in 3,718 elderly participants of the Chicago Health and Aging Project, followed for 5.5 years, evaluated the impact of fat and copper intakes using food frequency questionnaires and various cognitive assessments. For individuals with high intakes of saturated and *trans* fat, cognitive decline was greater for those in the highest quintile of total copper intake compared to the lowest quintile (median intake of 2.75 vs. 0.88 mg/day) (86).

Although a dysfunctional copper metabolism is suggested as a risk factor for AD, it could also be symptomatic of the disease. Moreover, it is still unclear whether copper supplementation or restriction could delay the progression of AD. A small, double-blind, placebo-controlled trial in 68 individuals with mild AD found that supplementation of 8 mg/day of copper for one year delayed the decrease of the β-amyloid peptide Aβ42 in cerebrospinal fluid; a decrease in Aβ42 has been linked to cognitive deterioration (87). However, this delay was not associated with improved cognitive performance (88). Based on the utilization of copper-chelating agents in Wilson's disease, the recent use of slow-release zinc acetate (150 mg/day for six months) in a randomized, placebo-controlled study of 60 patients with mild to moderate AD resulted in a decrease in serum 'free' copper and stabilization of cognition deficits (81). Additional human studies are needed to clarify the role of copper in AD onset and progression, and to evaluate whether dietary copper might help prevent AD in high-risk individuals or manage the disease in AD patients.

Parkinson's disease

Both neurologically presenting Wilson's disease and inherited aceruloplasminemia are characterized by copper accumulation in the brain, resulting in neurologic symptoms (dystonia and cognitive impairment) that resemble Parkinson's disease (PD) (89). The level of copper is diminished in brain regions of neuronal loss in PD patients (90). However, the recent meta-analysis of studies measuring copper levels in serum, plasma, and cerebrospinal fluid did not find any difference between PD patients and healthy elderly subjects (91).

Sources

Food sources

Copper is found in a wide variety of foods and is most plentiful in organ meats, shellfish, nuts, and seeds. Wheat-bran cereals and whole-grain products are also good sources of copper. According to national surveys, the average dietary intake of copper in the US is approximately 1.0 to 1.1 mg (1,000 to 1,100 μg) per day for adult women and 1.2 to 1.6 mg (1,200 to 1,600 μg) per day for adult men (15). The copper content of some foods that are relatively rich in copper is listed in micrograms (μg) in **Table 2**. For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Copper

Food	Serving	Copper (μg)
Liver (beef), cooked, pan-fried	1 ounce	4,128
Mollusks, oysters, eastern, wild, cooked, moist heat	6 medium oysters	2,397

Mollusks, oysters, eastern, wild, cooked, moist heat	6 medium oysters	2,397
Crab meat, Alaskan king, cooked	3 ounces	1,005
Crab meat, blue, cooked, moist heat	3 ounces	692
Mollusks, clams, mixed species, cooked, moist heat	3 ounces	585
Cashews nuts, raw	1 ounce	622
Sunflower seed kernels, dry roasted	1 ounce	519
Hazelnuts, dry roasted	1 ounce	496
Almonds	1 ounce	292
Peanut butter, chunk style, without salt	2 tablespoons	185
Lentils, mature seeds, cooked, boiled, without salt	1 cup	497
Mushrooms, white, raw	1 cup (sliced)	223
Shredded wheat cereal	2 biscuits	167
Chocolate (semisweet)	1 ounce	198

Supplements

Copper supplements are available as cupric oxide, copper gluconate, copper sulfate, and copper amino acid chelates (92).

Safety

Toxicity

Copper toxicity is rare in the general population. Acute copper poisoning has occurred through the contamination of beverages by storage in copper-containing containers, as well as from contaminated water supplies (93). Guideline values for copper in drinking water have been set by the US Environmental Protection Agency (1.3 mg/liter) and by the World Health Organization (2 mg/liter) (94). Symptoms of acute copper toxicity include abdominal pain, nausea, vomiting, and diarrhea; such symptoms help prevent additional ingestion and absorption of copper. More serious signs of acute copper toxicity include severe liver damage, kidney failure, coma, and death. Of more concern from a nutritional standpoint is the possibility of liver damage resulting from long-term exposure to lower doses of copper. In generally healthy individuals, doses of up to 10,000 μg (10 mg) daily have not resulted in liver damage. For this reason, the US Food and Nutrition Board set the tolerable upper intake level (UL) for copper at 10 mg/day from food and supplements (15; **Table 3**). It should be noted that individuals with genetic disorders affecting copper metabolism (e.g., Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis) may be at risk for adverse effects of chronic copper toxicity at significantly lower intake levels. There is some concern that the UL of 10 mg/day might be too high. In particular, men in a research study consumed 7.8 mg/day of copper for 147 days. They accumulated copper during that time, and some indices of immune function and antioxidant status suggested that these functions were adversely affected by the high intakes of copper (95, 96). However, another study did not report any adverse effects in individuals supplemented with 8 mg/day of copper for six months (88).

Table 3. Tolerable Upper Intake Level (UL) for Copper

Age Group	UL (μg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	1,000
Children 4-8 years	3,000
Children 9-13 years	5,000
Adolescents 14-18 years	8,000
Adults 19 years and older	10,000
*Source of intake should be from food and formula only.	

Drug interactions

Relatively little is known about the interaction of copper with drugs. Penicillamine is used to bind copper and enhance its elimination in Wilson's disease, a genetic disorder resulting in hepatic copper overload. Because penicillamine dramatically increases the urinary excretion of copper, individuals taking the medication for reasons other than copper overload may have an increased copper requirement.

Linus Pauling Institute Recommendation

The RDA for copper (900 μg/day for adults) is sufficient to prevent deficiency, but the lack of clear indicators of copper nutritional status in humans makes it difficult to determine the level of copper intake most likely to promote optimum health or prevent chronic disease. A varied diet should provide enough copper for most people. For those who are concerned that their diet may not provide adequate copper, a multivitamin/mineral supplement will generally provide at least the RDA for copper.

Older adults (>50 years)

Because aging has not been associated with significant changes in the requirement for copper, our recommendation for older adults is the same as that for adults 50 and younger (97).

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Fluoride

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Español

Summary

- Fluoride is the ionic form of the naturally occurring fluorine element. The anion increases the structural stability of teeth and bones through interactions with calcium phosphates. *(More information)*
- The daily intake recommendations for fluoride are based on the safest and most effective intakes to prevent dental caries. *(More information)*
- The use of fluoridated dental products and adequate intakes of fluoride reduce the occurrence of caries throughout life by promoting tooth mineralization and re-mineralization. Large randomized, placebo-controlled studies are needed to evaluate whether the topical application of fluoridated agents could also prevent dental erosion. *(More information)*
- Epidemiological and clinical evidence is currently limited to support a role for water fluoridation in the prevention of osteoporosis and bone fracture. *(More information)*
- Therapeutic trials have found a dose-dependent effect of fluoride on fracture risk in osteoporotic patients. However, the occurrence of numerous side effects warrants additional studies to guarantee that safe and effective doses can be used alone or in combination with current therapies. *(More information)*
- The major sources of systemic and topical fluoride are drinking water, foods and beverages made with fluoridated water, infant formulas, and fluoride-containing oral care products. Fluoridated salt and milk are currently available outside the US in Europe, Latin America, and Southeast Asia. *(More information)*
- While increased exposure to fluoride has led to a decline in dental caries, the prevalence of white speckling or mottling of the permanent teeth, known as dental fluorosis, has increased. Bone tissue homeostasis may also be affected by excess fluoride intake. *(More information)*

Fluorine occurs naturally as the negatively charged ion, fluoride (F^-). Fluoride is considered a trace element because only small amounts are present in the body (about 2.6 grams in adults), and because the daily requirement for maintaining dental health is only a few milligrams a day. About 95% of the total body fluoride is found in bones and teeth (1). Although its role in the prevention of dental caries (tooth decay) is well established, fluoride is not generally considered an essential mineral element because humans do not require it for growth or to sustain life (2). However, if one considers the prevention of chronic disease (dental caries) an important criterion in determining essentiality, then fluoride might well be considered an essential trace element (3).

Function

Fluoride is absorbed in the stomach and small intestine. Once in the bloodstream it rapidly enters mineralized tissue (bones and developing teeth). At usual intake levels, fluoride does not accumulate in soft tissue. The predominant mineral elements in bone are crystals of calcium and phosphate, known as hydroxyapatite crystals. Fluoride's high chemical reactivity and small radius allow it to either displace the larger hydroxyl (-OH) ion in the hydroxyapatite crystal, forming fluoroapatite, or to increase crystal density by entering spaces within the hydroxyapatite crystal. Fluoroapatite hardens tooth enamel and stabilizes bone mineral (4).

Nutrient interactions

Both calcium and magnesium form insoluble complexes with fluoride and are capable of significantly decreasing fluoride absorption when present in the same meal. However, the absorption of fluoride in the form of monofluorophosphate (unlike sodium fluoride) is unaffected by calcium. Also, a diet low in chloride (salt) has been found to increase fluoride retention by reducing urinary excretion of fluoride (1).

Deficiency

In humans, the only clear effect of inadequate fluoride intake is an increased risk of dental caries (tooth decay) for individuals of all ages. Epidemiological investigations of patterns of water consumption and the prevalence of dental caries across various US regions with different water fluoride concentrations led to the development of a recommended optimum range of fluoride concentration of 0.7-1.2 milligrams/liter (mg/L) or parts per million (ppm); the lower concentration was recommended for warmer climates where water consumption is higher, and the higher concentration was recommended for colder climates. In 2015, the US Department of Health and Human Services recommended that all community water systems adjust the fluoride concentration to 0.7 mg/L, as more recent studies did find a relationship between water intake and outdoor air temperature. This recommendation was made in an effort to reduce the risk of dental fluorosis (see below) and in light of the widespread availability of fluoride from other sources, including fluoride-containing oral-care products (5). A number of studies conducted prior to the introduction of fluoride-containing toothpastes demonstrated that the prevalence of dental caries was 40% to 60% lower in communities with optimal water fluoride concentrations than in communities with low water fluoride concentrations (6).

The Adequate Intake (AI)

The Food and Nutrition Board (FNB) of the US Institute of Medicine updated its recommendations for fluoride intake in 1997. Because data were insufficient to establish a Recommended Dietary Allowance (RDA), Adequate Intake (AI) levels were set based on estimated intakes that have been shown to reduce the occurrence of dental caries most effectively without causing the unwanted side effect of tooth enamel mottling known as dental fluorosis (0.05 mg/kg of body weight) (**Table 1**; 6). See the section below on Safety for a discussion of dental fluorosis.

Table 1. Adequate Intake (AI) for Fluoride

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.01	0.01
Infants	7-12 months	0.5	0.5
Children	1-3 years	0.7	0.7
Children	4-8 years	1.0	1.0
Children	9-13 years	2.0	2.0
Adolescents	14-18 years	3.0	3.0
Adults	19 years and older	4.0	3.0
Pregnancy	all ages	-	3.0
Breast-feeding	all ages	-	3.0

Disease Prevention

Dental caries (cavities and tooth decay)

Specific cariogenic (cavity-causing) bacteria (mainly *Streptococcus mutans* and *Streptococcus sobrinus*) found in dental plaque are capable of metabolizing fermentable carbohydrates (sugars) and converting them to organic acids that can dissolve sensitive tooth enamel. If unchecked, the bacteria may penetrate deeper layers of the tooth and progress into the soft pulp tissue at the center. Untreated caries can lead to severe pain, local infection, tooth loss or extraction, nutritional problems, and serious systemic infections in susceptible individuals (7). Dental caries — both treated and untreated — contribute to diminished overall oral health, which, in turn, may affect systemic health. For example, some observational studies have suggested a link between systemic inflammation in individuals with periodontal (gum) infection and insulin resistance (8), type 2 diabetes mellitus (9), hypertension (10), and coronary heart disease (11). Moreover, the bacterium causing periodontitis, *Porphyromonas gingivalis*, may be linked to rheumatoid arthritis (12, 13). Poor oral health in general may constitute a risk factor for coronary heart disease (14) and other cardiovascular diseases (15, 16).

Systemic effects of fluoride on teeth

Increased fluoride exposure, most commonly through community water fluoridation, has been found to decrease the incidence of dental caries in children and adults (17, 18). Between 1976 and 1987, clinical studies in several countries demonstrated that the addition of fluoride to community water supplies (0.7-1.2 ppm) reduced caries by 30%-60% in primary (baby) teeth and 15%-35% in permanent teeth (19). A 2015 review and meta-analysis of prospective observational studies found a 35% and 26% reduction in number of decayed, missing, and filled primary and permanent teeth with consumption of fluoridated versus non-fluoridated water, respectively (20). While fluoride's prevention of dental caries is primarily through topical action, fluoride consumed in water appears to have a systemic effect in children before all teeth have erupted — typically through 12 years of age.

Fluoride is incorporated into the developing enamel of teeth and increases the resistance to caries. Since the caries preventative effect of fluoride is also topical (surface) in children after teeth have erupted and in adults, the optimal protection achieved by fluoridated water likely occurs through both systemic exposure before and after tooth eruption and topical exposure after tooth eruption.

Topical effects of fluoride on teeth

Research has indicated that the primary action of fluoride occurs topically after the teeth erupt into the mouth. Ingested fluoride is secreted in the saliva and contributes to topical protection. When enamel is partially demineralized by organic acids, fluoride in the saliva can enhance the remineralization of enamel through its interactions with calcium and phosphate. Fluoride containing remineralized enamel is more resistant to acid attack and demineralization. In salivary concentrations associated with optimum fluoride intake, fluoride has been found to inhibit bacterial enzymes, resulting in reduced acid production by cariogenic bacteria (7, 17).

The use of topically applied fluoride-containing products, including toothpaste, gel, varnish, and mouth rinse, is thought to have contributed to the substantial decrease in the prevalence of caries over the last decades (21). A 2013 meta-analysis of fluoride interventions in children and adolescents (up to 16 years of age) found that the application of fluoride varnish for at least one year was associated with a 37% reduction in decayed, missing, and filled tooth surfaces in decayed tooth surfaces of primary teeth; the anti-caries effect on the permanent teeth corresponded to a 43% decrease compared to no treatment or placebo (22). A recent (2021) meta-analysis of topical fluoride reviewed 15 clinical trials with 9,541 participants. Specifically, the meta-analysis evaluated 14 trials of fluoride varnish compared to placebo or no fluoride and one trial of fluoride foam, and found that topical fluoride reduced dental caries increment by about one tooth surface over a two-year period (23). The same meta-analysis also found that fluoride varnish significantly prevented any incident dental caries, but only for children who were younger than 2 years of age (23).

The effects of fluoride-containing toothpaste has been more extensive. A 2017 meta-analysis of 96 randomized controlled trials, including more than 65,000 participants, found tooth brushing with a fluoridated toothpaste reduced caries in primary teeth of children and in permanent teeth of adults compared to brushing with non-fluoridated toothpaste (24). In participants overall, use of toothpastes containing 1,000 to 1,500 ppm of fluoride had a caries-preventative effect compared to use of toothpastes with lower fluoride concentrations or with non-fluoridated toothpastes (24). A systematic review of 17 clinical trials found use of fluoridated toothpaste effectively reduced dental caries in primary teeth of children younger than 6 years who were at high risk of developing dental caries (25).

Dental erosion (tooth wear)

The attack of dental hard tissue by acids other than those produced by the bacterial plaque may lead to the loss of tooth enamel, also known as dental erosion. Factors involved in dental erosion include acidic foods and beverages (e.g., carbonated drinks) and acid reflux (26). The protective effect of fluoridated agents against dental erosion has mainly been observed in *in vitro* studies (reviewed in 26). Nevertheless, a meta-analysis of four small, randomized trials examining the effect of fluoride in toothpaste, varnish, and saliva on dental erosion did not find any overall benefit compared to placebo (27). Larger clinical studies are needed to evaluate whether topical fluoride applications can prevent dental erosion and/or reduce the progression of existing erosive lesions.

Osteoporosis

Although fluoride in pharmacologic doses has been shown to be a potent therapeutic agent for increasing spinal bone mass (see Disease Treatment), there is little evidence that water fluoridation at optimum levels for the prevention of dental caries is helpful in the prevention of osteoporosis. The majority of studies conducted to date have failed to find clinically significant differences in bone mineral density (BMD) or fracture incidence when comparing residents of areas with fluoridated water supplies to residents in areas without fluoridated water supplies (28, 29). However, two studies found that drinking water fluoridation was associated with decreased incidence of hip fracture in the elderly. In addition, one study in Italy found a significantly greater risk of femoral (hip) fractures in men and women residing in an area with low water fluoridation (0.05 ppm) compared to the risk in a similar population whose water supply was naturally fluoridated (1.45 ppm) at higher than optimum levels for prevention of dental caries (30). Another study in Germany found no significant difference in BMD between residents of a community whose water supply had been optimally fluoridated for 30 years (1 ppm) compared with those who resided in a community without fluoridated water. However, this study reported that the incidence of hip fracture in men and women, aged 85 years or older, was significantly lower in the community with fluoridated water compared to the community with non-fluoridated water, despite higher calcium levels in the non-fluoridated water supply (31). Another community-based study in 1,300 women found that elevated serum fluoride concentrations were not related to BMD or to osteoporotic fracture incidence (32). Finally, a nationwide cohort study in Sweden found no association between chronic exposure to fluoridated water and incidence of hip fracture (33). A 2015 meta-analysis, which pooled results of 13 prospective cohort studies and one case-control study, found that fluoride exposure in drinking water was not associated with risk of hip fracture (34).

Moreover, because bone mineral accretion early in life affects risk for osteoporosis in later adulthood, studies have examined the association of fluoride intake during adolescence and bone outcomes. Reports from the Iowa Bone Development Study, an ongoing prospective cohort study, indicate little to no association of fluoride intake during childhood and adolescence with measures of bone microstructure throughout adolescence (35-37) and into early adulthood (38).

Disease Treatment

Osteoporosis

Osteoporosis is characterized by decreased bone mineral density (BMD) and increased bone fragility and susceptibility to fracture. In general, decreased BMD is associated with increased risk of fracture. However, the usual relationship between BMD and fracture risk does not always hold true when very high (pharmacologic) doses of fluoride are used to treat osteoporosis. Most available therapies for osteoporosis (e.g., estrogen, calcitonin, and bisphosphonates) decrease bone loss (resorption), resulting in very small increases in BMD. Pharmacologic doses of fluoride are capable of producing large increases in the BMD of the lumbar spine. Overall, therapeutic trials of fluoride in patients with osteoporosis have not consistently demonstrated significant decreases in the occurrence of vertebral fracture despite dramatic increases in lumbar spine BMD (39). A meta-analysis of 11 controlled studies, including 1,429 participants, found that fluoride treatment resulted in increased BMD at the lumbar spine but was not associated with a lower risk of vertebral fractures (40). This meta-analysis also found that higher concentrations of fluoride were associated with increased risk of non-vertebral fractures after four years of treatment. Early studies using high doses of fluoride (>20 mg/day) may have induced rapid bone mineralization in the absence of adequate calcium and vitamin D, resulting in denser bones that were not mechanically stronger (41, 42). Analysis of bone architecture has also shed some light on the inconsistent effect of fluoride therapy in reducing vertebral fractures. Research has indicated that osteoporosis may be associated with an irreversible change in the architecture of bone known as decreased trabecular connectivity. Normal bone consists of a series of plates interconnected by thick rods. Severely osteoporotic bone has fewer plates, and the rods may be fractured or disconnected (decreased trabecular connectivity) (43). Despite fluoride therapy increasing bone density, it probably cannot reduce bone resorption and restore connectivity in patients with severe bone loss. Thus, fluoride therapy may be less effective in osteoporotic individuals who have already lost substantial trabecular connectivity (39, 44).

On the other hand, randomized controlled trials using lower fluoride doses (≤20 mg/day), intermittent dosage schedules, or slow-release formulations (enteric coated sodium fluoride) have demonstrated a decreased incidence of vertebral and non-vertebral fractures along with increased bone density of the lumbar spine (45). Yet, bone biopsies from postmenopausal, osteoporotic women treated with 20 mg/day of fluoride showed evidence of abnormal bone mineralization despite calcium and vitamin D supplementation (46). Additionally, a randomized, double-blind, placebo-controlled study did not find any increase in lumbar spine BMD in 180 postmenopausal women with osteopenia (early osteoporosis) who were given daily supplements of up to 10 mg/day of fluoride for one year (47). Additional studies are required to assess whether a safe dose of fluoride can be found to maximize bone formation while preventing mineralization defects.

Safety of fluoride therapy for osteoporosis

Serious side effects have been associated with the high doses of fluoride used to treat osteoporosis (45). They include gastrointestinal irritation, joint pain in the lower extremities, and the development of calcium deficiency and stress fractures. The reasons for the occurrence of lower extremity joint pain and stress fractures in patients taking fluoride for osteoporosis remain unclear, but they may be related to rapid increases in bone formation without sufficient calcium to support such an increase (39). Presently, enteric coated sodium fluoride or monofluorophosphate preparations offer a lower side effect profile than the high-dose sodium fluoride used in earlier trials. Additionally, sufficient calcium and vitamin D must be provided to support fluoride-induced bone formation. Although fluoride therapy may be beneficial for the treatment of osteoporosis in appropriately selected and closely monitored individuals, uncertainty about its safety and benefit in reducing fractures has kept the US Food and Drug Administration (FDA) from approving fluoride therapy for osteoporosis (48). Combinations of lower doses of fluoride with antiresorptive agents, such as estrogen or bisphosphonates, may improve therapeutic results while minimizing side effects (49, 50). Yet, randomized studies have shown that the risk of fractures remained unchanged whether treatments include fluoride, antiresorptives, or both (45, 46). Additional studies are warranted to determine whether any treatment combinations could provide substantial therapeutic benefits over monotherapy.

Sources

Water fluoridation

The major source of dietary fluoride in the US diet is drinking water. Controlled addition of fluoride to water is used by communities as a public health measure to adjust fluoride concentration in drinking water to prevent dental caries. Originally, an optimal range of 0.7 to 1.2 milligrams (mg) per liter (corresponding to 0.7-1.2 ppm) was established, which was shown to decrease the incidence of dental caries while minimizing the risk of dental fluorosis and other adverse effects. In 2015, the US Department of Health and Human Services recommended that the optimal concentration in drinking water be set at 0.7 ppm (see Safety) (51). Approximately 73% of the US population receives water with sufficient fluoride for the prevention of dental caries (52). The average fluoride intake for adults living in fluoridated communities ranges from 1.4 to 3.4 mg/day compared to 0.3 to 1 mg/day in non-fluoridated areas (6). Since well water can vary greatly in its fluoride content, people who consume water from wells should have the fluoride content of their water tested by their local water district or health department. Water fluoride testing may also be warranted in households that use home water treatment systems. While water softeners are not thought to change water fluoride levels, reverse osmosis systems, distillation units, and some water filters have been found to remove significant amounts of fluoride from water. However, Brita-type carbon-charcoal filters do not remove fluoride (6, 48).

Bottled water sales have grown exponentially in the US in the last decades, and studies have found that most bottled waters contain sub-optimal levels of fluoride, although there is considerable variation (53). For example, a study of 105 different bottled water products in the Greater Houston metropolitan area found that over 80% had fluoride concentrations of less than 0.4 ppm; only 5% of the tested products had fluoride concentrations within the recommended range (54). Several other studies have reported similar findings, with most bottled waters relatively low in fluoride, but a few in the optimal range or higher (55-57). The FDA-approved claim that "drinking fluoridated water may reduce the risk of tooth decay" is only used by bottlers when the water contains greater than 0.6 ppm of fluoride but no more than 1.0 ppm of fluoride. However, bottlers are not required to provide the fluoride concentration in bottled water unless fluoride was added (58).

Infant formulas

While consumption of fluoride from water presents very little risk of adverse effects in adults except in extreme circumstances (see Safety), consumption of relatively large amounts of water mixed with formula concentrates appears to increase the risk for the development of dental fluorosis in infants (59-61). One study found that, on average, at least half of all fluoride ingested by infants 6 months and younger was from water mixed with formula concentrates (62). The study of 49 commercially available infant formulas in the Chicago area showed that milk-based ready-to-feed, liquid concentrate, and powdered formulas (reconstituted with deionized water) had mean fluoride concentrations of 0.15 ppm, 0.27 ppm, and 0.12 ppm, respectively (63). Fluoride content was significantly higher in soy-based compared to milk-based liquid concentrate formulas (0.50 ppm vs. 0.27 ppm). Using average body weights and total formula intakes during the first year of life, the authors estimated that the risk of exceeding the tolerable upper intake level (UL) for fluoride ingestion was minimal when liquid concentrate and powdered formulas were reconstituted with water containing less than 0.5 ppm of fluoride, but the risk was maximal with 1.0 ppm fluoridated water. Fluoride-free or low-fluoride water labeled as "deionized," "purified," "demineralized," "distilled," or "produced through reverse-osmosis" can be used in order to minimize the risk for mild fluorosis (58). However, infants between 6 and 12 months may not reach the adequate intake of fluoride if they are fed ready-to-feed formulas or formulas reconstituted with water containing less than 0.4 ppm (63).

For additional information on fluoride and infant formulas, see the CDC website.

Food and beverage sources

The fluoride content of most foods is low (less than 0.05 mg/100 grams or 0.5 ppm). Rich sources of fluoride include tea, which concentrates fluoride in its leaves, and marine fish that are consumed with their bones (e.g., sardines). Foods made with mechanically separated (boned) chicken, such as canned meats, hot dogs, and infant foods, also add fluoride to the diet (64). In addition, certain fruit juices, particularly grape juices, often have relatively high fluoride concentrations (65). Foods generally contribute only 0.3-0.6 mg of the daily intake of fluoride. An adult male residing in a community with fluoridated water has an intake range from 1 mg/day-3 mg/day. Intake is less than 1 mg/day in non-fluoridated areas (2). **Table 2** provides a range of fluoride content for a few fluoride-rich foods. For more information on the fluoride content of foods and beverages, search the USDA national fluoride database.

Table 2. Some Food Sources of Fluoride

Food	Serving	Fluoride (mg)	Fluoride (ppm)*
Black tea	100 mL (3.5 fluid ounces)	0.25-0.39	2.5-3.9
Fruit juice	100 mL (3.5 fluid ounces)	0.02-0.21	0.2-2.1
Crab (canned)	100 g (3.5 ounces)	0.21	2.1
Rice (cooked)	100 g (3.5 ounces)	0.04	0.4
Fish (cooked)	100 g (3.5 ounces)	0.02	0.2
Chicken	100 g (3.5 ounces)	0.015	0.15
*1.0 part per million (ppm) = 1 milligram/liter (mg/L)			

Fluoride supplements

Fluoride supplements — available only by prescription in the US — are intended for infants 6 months and older and children up to 16 years of age living in areas with suboptimal water fluoridation for the purpose of bringing their intake to approximately 1 mg/day (6). The American Dental Association Council on Scientific Affairs recommends the prescription of fluoride supplements only to children at high risk of developing dental caries (66). The supplemental fluoride dosage schedule in **Table 3** was recommended by the American Dental Association, the American Academy of Pediatric Dentistry, and the American Academy of Pediatrics (66, 67). It requires knowledge of the fluoride concentration of local drinking water, as well as other possible sources of fluoride intake. For more detailed information regarding fluoride and the prevention of dental caries, visit the American Dental Association website.

Table 3. American Dental Association Fluoride Supplement Schedule

Age	Fluoride Ion Level in Drinking Water (ppm)*		
	<0.3 ppm	0.3-0.6 ppm	>0.6 ppm
Birth - 6 months	None	None	None
6 months - 3 years	0.25 mg/day**	None	None
3 years - 6 years	0.50 mg/day	0.25 mg/day	None
6 years - 16 years	1.0 mg/day	0.50 mg/day	None
*1.0 part per million (ppm) = 1 milligram/liter (mg/L) **2.2 mg sodium fluoride contains 1 mg fluoride ion.			

Toothpaste

Fluoridated toothpastes (1,000-1,100 ppm of fluoride) are very effective in preventing dental caries but also add considerably to fluoride intake of children, especially young children who are more likely to swallow toothpaste. Researchers estimate that children under 6 years of age may ingest an average of 0.3 mg of fluoride from toothpaste with each brushing. Children under the age of 6 years who ingest more than two or three times the recommended fluoride intake are at increased risk of a white speckling or mottling of the permanent teeth, known as dental fluorosis (see Safety section below). A major source of excess fluoride intake in this age group comes from swallowing fluoride-containing toothpaste. To prevent dental fluorosis while providing optimum protection from tooth decay, it is recommended that parents supervise children under 6 years of age while brushing with fluoridated toothpaste. In addition to discouraging the swallowing of toothpaste, children should be supervised during teeth brushing, and young children should be encouraged to use very small amounts of toothpaste — a "smear amount" (a thin layer of toothpaste that covers less than half of the bristle surface of a child-size toothbrush; size equivalent to a grain of rice) for children younger than 3 years, and no more than a pea-sized application of toothpaste for children 3 to 6 years of age (25, 68-70). Interestingly, it has been suggested that the management of the fluorosis risk in young children who ingest fluoridated toothpaste could include the use of toothpaste formulation that reduces gastrointestinal absorption and bioavailability of fluoride (71).

Salt fluoridation

Fluoridation of salt has been implemented in several countries worldwide as an alternative to water fluoridation to promote the ingestion of fluoride and improve oral care. Since the fluoridation of water is extensively practiced in the US, fluoride is not added to salt. Observational studies have shown that the incidence of teeth with caries dramatically decreased in the regions where salt fluoridation programs were developed (reviewed in 72). While concerns around hypertension and the monitoring of population intakes should be addressed, no adverse health effects linked to the fluoridation of salt have been reported (reviewed in 73). According to the World Health Organization (WHO), salt fluoridation and, to a lesser extent, milk fluoridation, are affordable alternatives to improve oral hygiene in areas where access to oral health services is limited and fluoridation of public water is not feasible (74).

Mouth rinses

Mouth rinses that contain fluoride are available over-the-counter in the US. Such products often contain 0.05% sodium fluoride, which translates to about 1 mg of fluoride per 5 mL (one teaspoon) (70). Due to the risk of accidental ingestion, fluoride-containing mouth rinses are not recommended for young children (70).

Professionally applied fluoride products

Professionally applied fluoride products, including fluoride foams, gels, varnish, and silver diamine fluoride, are highly concentrated (9,000 to 44,800 ppm of fluoride) and applied topically to the teeth by dentists, dental hygienists, or other healthcare professionals (75). Because of their high concentrations, they are potential sources of fluoride; however, due to their infrequent use (every 3-6 months) and small amounts used per application, professionally applied fluoride products are not significant sources of fluoride when used as directed (75).

Safety

Adverse effects

Fluoridation of public drinking water in the US was initiated more than 70 years ago. Since then, a number of adverse effects have been attributed to water fluoridation. However, extensive scientific research has uncovered no evidence of increased risks of cancer, heart disease, kidney disease, liver disease, thyroid disease, Alzheimer's disease, birth defects, or Down's syndrome (51, 76, 77).

A number of observational studies, mostly published in Chinese journals, have investigated the association between fluoride content in drinking water and children's neurodevelopment. Two meta-analyses of observational studies, mainly conducted in China, found lower intelligence quotients (IQs) in children exposed to higher fluoride concentrations in drinking water (78, 79). Serious limitations, including substantial heterogeneity among studies and co-occurrence of neurotoxicants in drinking water, hinder the strength of these findings and their application to US settings. The Academy of Nutrition and Dietetics has estimated that only limited evidence supports an association between fluoride content in water and the IQs of children (58). A prospective study in a New Zealand population-based cohort followed for nearly four decades found no association between fluoride exposure in the context of community water fluoridation programs and IQs measured during childhood and at age 38 years (80). A series of recent studies by a research group in Canada have raised concern over a possible link between higher maternal fluoride exposures during pregnancy and lower IQ (81-83), cognitive delay (84), and attention-deficit/hyperactivity disorder (85) in offspring. However, these studies have been widely criticized for shortcomings in measuring fluoride intake, only reporting significant relationships among subgroups, and being observational and subject to residual confounding. Thus, high-quality prospective studies with more definitive fluoride intake measures and better control of confounders are needed to determine whether fluoride might have neurotoxic effects at usual intake levels.

Acute toxicity

Fluoride is toxic when consumed in excessive amounts, so concentrated fluoride products should be used and stored with caution to prevent the possibility of acute fluoride poisoning, especially in children and other vulnerable individuals. The lowest dose that could trigger adverse symptoms is considered to be 5 mg/kg of body weight, with the lowest potentially fatal dose considered 15 mg/kg of body weight. Nausea, abdominal pain, and vomiting almost always accompany acute fluoride toxicity. Other symptoms like diarrhea, excessive salivation and tearing, sweating, and generalized weakness may also occur (77). In order to prevent acute fluoride poisoning, the American Dental Association has recommended that no more than 120 mg of fluoride (224 mg of sodium fluoride) be dispensed at one time (48). The use of high doses of fluoride to treat osteoporosis has been associated with some adverse effects, which are discussed in the Disease Treatment section above.

Dental fluorosis

Dental fluorosis, also called enamel fluorosis, is a result of excess fluoride intake during the period of tooth formation, with the critical window of susceptibility being the first eight years of life, as this corresponds to the eruption of the permanent teeth (86). Once the tooth enamel has formed, dental fluorosis cannot develop (87). The mildest form of dental fluorosis is detectable only to the trained observer and is characterized by small opaque white flecks or spots on the enamel of the teeth. Moderate dental fluorosis is characterized by mottling and mild staining of the teeth, and severe dental fluorosis results in marked staining and pitting of the teeth. In its moderate to severe forms, dental fluorosis becomes a cosmetic concern when it affects the incisors and canines (front teeth). Dental fluorosis is a dose-dependent condition, with higher fluoride intakes being associated with more pronounced effects on the teeth.

The incidence of mild and moderate dental fluorosis has increased over the past decades, mainly due to increasing fluoride intake from reconstituted infant formula and toothpaste, although inappropriate use of fluoride supplements may also contribute (61). According to a US national survey, the National Health and Nutrition Examination Survey (NHANES) 1999-2004, 23% of people aged 6 to 49 years (n=16,051) had some degree of dental fluorosis (88). National data from NHANES 2011-2012 found that the prevalence of fluorosis among children and adolescents (n=2,283), ages 6 to 19 years, was much higher at 57% (89); however, a quality assessment of these data raised concerns about their validity and suggested such results were not biologically plausible (90). In 1997, the US Food and Nutrition Board (FNB) of the Institute of Medicine set the tolerable upper intake level (UL) for fluoride based on the prevention of moderate enamel fluorosis (**Table 4**) (6).

Table 4. Tolerable Upper Intake Level (UL) for Fluoride

Age Group	UL (mg/day)
Infants 0-6 months	0.7
Infants 7-12 months	0.9
Children 1-3 years	1.3
Children 4-8 years	2.2
Children 9-13 years	10.0
Adolescents 14-18 years	10.0
Adults 19 years and older	10.0

The current US EPA maximum allowable level of fluoride in drinking water is 4 mg/L; the EPA also has a non-enforceable standard fluoride level of 2 mg/L to prevent moderate dental fluorosis (91). The EPA recently conducted a six-year review of drinking water standards and concluded that the limit of fluoride in drinking water is not a candidate for regulatory revision at this time (92).

Skeletal fluorosis

Intake of fluoride at excessive levels for long periods of time may lead to changes in bone structure known as skeletal fluorosis. The early stages of skeletal fluorosis are characterized by increased bone mass, detectable by x-ray. If very high fluoride intake persists over many years, joint pain and stiffness may result from the skeletal changes. The most severe form of skeletal fluorosis is known as "crippling skeletal fluorosis," which may result in calcification of ligaments, immobility, muscle wasting, and neurological problems related to spinal cord compression. While skeletal fluorosis is endemic in many world regions with naturally high fluoride concentrations in drinking water, crippling skeletal fluorosis may occur only when fluoride intake exceeds 10 mg/day for at least 10 years (6, 93). Rare cases of skeletal fluorosis in the US have been observed in consumers of large volumes of tea (94-97). Because of the potential risk for skeletal fluorosis, as well as the risks for pitting of tooth enamel and bone fracture, the US EPA set the maximum level of fluoride allowed in drinking water at 4 mg/L (98). The agency also recommended limiting fluoride in drinking water at 2 mg/L to prevent dental fluorosis in children; however, this is only a guideline and not enforceable by law (see the US EPA website).

Drug interactions

Calcium supplements, as well as calcium and aluminum-containing antacids, can decrease the absorption of fluoride. It is best to take these products two hours before or after fluoride supplements (99).

Linus Pauling Institute Recommendation

The safety and public health benefits of optimally fluoridated water for prevention of tooth decay in people of all ages have been well established. The Linus Pauling Institute supports the recommendations of the American Dental Association and the Centers for Disease Control and Prevention, which include optimally fluoridated water and the use of fluoride toothpaste, fluoride mouth rinse, fluoride varnish, and when necessary, fluoride supplementation. Due to the risk of fluorosis, any fluoride supplementation should be prescribed and closely monitored by a dentist or physician.

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Iodine

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Summary

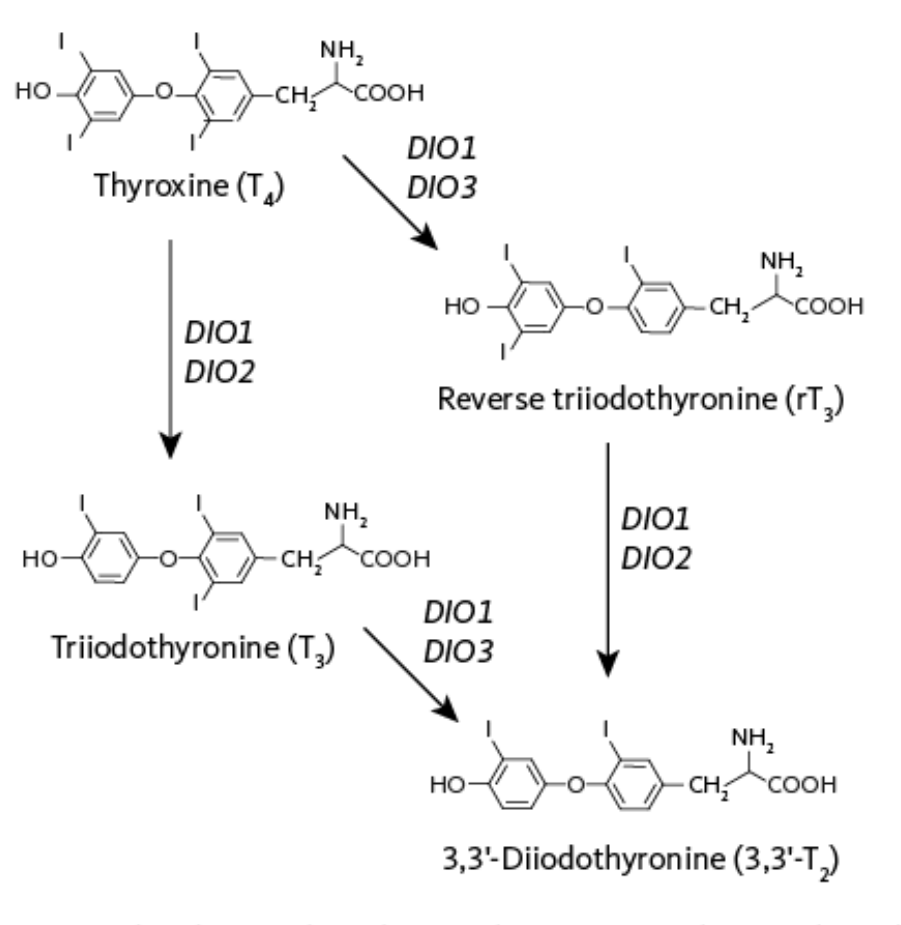
- Iodine is a key component of thyroid hormones, which are required throughout life for normal growth, neurological development, and metabolism. *(More information)*
- Insufficient iodine intake impairs the production of thyroid hormones, leading to a condition called hypothyroidism. Iodine deficiency results in a range of adverse health disorders with varying degrees of severity, from thyroid gland enlargement (goiter) to severe physical and mental retardation known as cretinism. *(More information)*
- Iodine deficiency-induced hypothyroidism has adverse effects in all stages of development but is most damaging to the developing brain. Maternal iodine deficiency during pregnancy can result in maternal and fetal hypothyroidism, as well as miscarriage, preterm birth, and neurological impairments in offspring. *(More information)*
- Even in areas with voluntary/mandatory iodization programs and in iodine-replete countries, pregnant women, lactating mothers, and young infants are among the most vulnerable to iodine deficiency due to their special requirements during these life stages. *(More information)*
- The recommended dietary allowance (RDA) for iodine intake is 150 micrograms (μg)/day in adults, 220 μg/day in pregnant women, and 290 μg/day in breast-feeding women. During pregnancy and lactation, the fetus and infant are entirely reliant on maternal iodine intake for thyroid hormone synthesis. *(More information)*
- Thyroid accumulation of radioactive iodine (^{131}I) increases the risk of developing thyroid cancer, especially in children. In case of radiation emergencies, current preventive measures include the distribution of pharmacologic doses of potassium iodide that would reduce the risk of significant uptake of ^{131}I by the thyroid gland. *(More information)*
- Seafood is an excellent source of dietary iodine. Dairy products, grains, eggs, and poultry contribute substantially to dietary iodine intakes in the US. *(More information)*
- More than 120 countries worldwide have introduced programs of salt fortification with iodine in order to correct iodine deficiency in populations. *(More information)*
- In iodine-deficient populations, a rapid increase in iodine intake may precipitate iodine-induced hyperthyroidism. The risk of iodine-induced hyperthyroidism is especially high in older people with multi-nodular goiter. *(More information)*
- In iodine-sufficient adults, long-term iodine intake above the tolerable upper intake level (UL) of 1,100 μg/day may increase the risk of thyroid disorders, including iodine-induced goiter and hypothyroidism. *(More information)*

Iodine (I), a non-metallic trace element, is required by humans for the synthesis of thyroid hormones. Iodine deficiency is an important health problem throughout much of the world. Most of the Earth's iodine, in the form of the iodide ion (I^-), is found in oceans, and iodine content in the soil varies with region. The older an exposed soil surface, the more likely the iodine has been leached away by erosion. Mountainous regions, such as the Himalayas, Atlas, Andes, and Alps; flooded river valleys, such as the Ganges River plain in India; and many inland regions, such as central Asia and Africa, central and eastern Europe, and the Midwestern region of North America are among the most severely iodine-deficient areas in the world (1).

Function

Iodine is an essential component of the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), and is therefore essential for normal thyroid function. To meet the body's demand for thyroid hormones, the thyroid gland traps iodine from the blood and incorporates it into the large (660 kDa) glycoprotein thyroglobulin. The hydrolysis of thyroglobulin by lysosomal enzymes gives rise to thyroid hormones that are stored and released into the circulation when needed. In target tissues, such as the liver and the brain, T_4 (the most abundant circulating thyroid hormone) can be converted to T_3 by selenium-containing enzymes known as iodothyronine deiodinases (DIOs) (**Figure 1**; see also Nutrient interactions). T_3 is the physiologically active thyroid hormone that can bind to thyroid receptors in the nuclei of cells and regulate gene expression. In this manner, thyroid hormones regulate a number of physiologic processes, including growth, development, metabolism, and reproductive function (2).

Figure 1. Deiodination of Thyroid Hormones

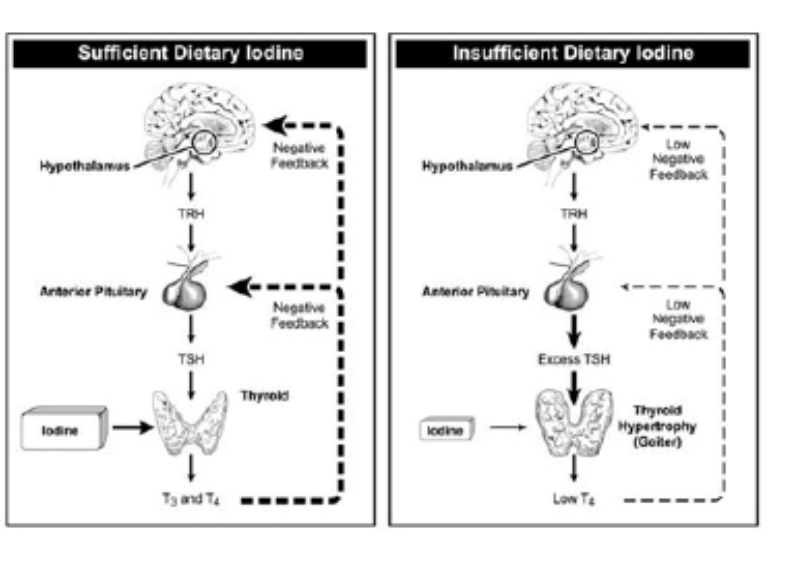


Iodothyronine deiodinases (DIOs) are selenoenzymes that catalyze the deiodination (removal of iodine) from iodothyronines. Specifically, DIO1 and DIO2 catalyze the deiodination of thyroxine (T_4) that generates the biologically active triiodothyronine (T_3). DIO3 inactivates T_3 and T_4 by removing iodine atoms from the inner ring.

[Figure 1 - Click to Enlarge]

The regulation of thyroid function is a complex process that involves the hypothalamus and the pituitary gland. In response to thyrotropin-releasing hormone (TRH) secretion by the hypothalamus, the pituitary gland secretes thyroid-stimulating hormone (TSH), which stimulates iodine trapping, thyroid hormone synthesis, and release of T_4 and T_3 by the thyroid gland. The presence of adequate circulating T_4 and T_3 feeds back at the level of both the hypothalamus and pituitary, decreasing TRH and TSH production (**Figure 2**). When circulating T_4 levels decrease, the pituitary gland increases its secretion of TSH, resulting in increased iodine trapping, as well as increased production and release of both T_3 and T_4. Iodine deficiency results in inadequate production of T_4. In response to decreased blood T_4 concentrations, the pituitary gland increases its output of TSH. Persistently elevated TSH levels may lead to hypertrophy (enlargement) of the thyroid gland, also known as goiter (see Deficiency) (3).

Figure 2. The Hypothalamic-Pituitary-Thyroid Axis



In response to thyrotropin-releasing hormone (TRH) secretion by the hypothalamus, the pituitary gland secretes thyroid-stimulating hormone (TSH). TSH stimulates iodine trapping and thyroid hormone synthesis by the thyroid gland and the release of T_3 (triiodothyronine) and T_4 (thyroxine) into the circulation.

When dietary iodine intake is sufficient, the presence of adequate serum T_4 and T_3 concentrations feeds back at the level of both the hypothalamus and pituitary gland, decreasing TRH and TSH production.

When circulating T_4 concentrations decrease, the pituitary gland increases its secretion of TSH, stimulating iodine trapping and production and release of both T_3 and T_4. In the case of iodine deficiency, persistently elevated TSH levels may lead to hypertrophy of the thyroid gland, also known as goiter.

[Figure 2 - Click to Enlarge]

Deficiency

The thyroid gland of a healthy adult concentrates 70-80% of a total body iodine content of 15-20 mg and utilizes about 80 μg of iodine daily to synthesize thyroid hormones. In contrast, chronic iodine deficiency can result in a dramatic reduction of the iodine content in the thyroid well below 1 mg (1). Iodine deficiency is recognized as the most common cause of preventable brain damage in the world. The spectrum of iodine deficiency disorders (IDD) includes mental retardation, hypothyroidism, goiter, and varying degrees of other growth and developmental abnormalities (4). The World Health Organization (WHO) estimated that over 30% of the world's population (2 billion people) have insufficient iodine intake as measured by median urinary iodine concentrations below 100 μg/L (5). Moreover, about one-third of school-age children (6-12 years old) worldwide (241 million children in 2011) have insufficient iodine intake (6, 7). Major international efforts have produced dramatic improvements in the correction of iodine deficiency in the 1990s, mainly through the use of iodized salt in iodine-deficient countries (4). Although about 70% of households in the world now have access to iodized salt (8), mild-to-moderate iodine deficiency remains a public health concern in at least 30 countries; there are no iodine excretion data available for 42 other countries, including Israel, Syria, and Sierra Leone (7). For more information on the international effort to eradicate iodine deficiency, visit the websites of the Iodine Global Network (formerly the International Council for the Control of Iodine Deficiency Disorders) and the WHO.

Biomarkers of iodine status

More than 90% of ingested iodine is excreted in the urine within 24-48 hours such that daily iodine intakes in a population can be extrapolated from measures of median spot urinary iodine concentrations (9, 10). According to WHO criteria, population iodine deficiency is defined by median urinary iodine concentrations lower than 150 micrograms (μg)/L for pregnant women and 100 μg/L for all other groups (**Table 1**). Adequate intakes correspond to median urinary iodine concentrations of 100-199 μg/L in school-age children and 150-249 μg/L in pregnant women (**Table 1**). While median urinary iodine concentration is a population indicator of recent dietary iodine intake, multiple collections of 24-hour urinary iodine are preferable to estimate intake in individuals (9-11).

Table 1. WHO Criteria for Assessment of Iodine Nutrition through Population-based Median Urinary Iodine Concentrations (4)

Population Group	Median/Range of Urinary Iodine Concentrations (μg/L)	Iodine Intake
Children (<2 years)	<100	Insufficient
	≥100	Adequate
Children (≥6 years), adolescents, and adults*	<100	Insufficient
	100-199	Adequate
	200-299	More than adequate
	>300	Excessive
Pregnant women	<150	Insufficient
	150-249	Adequate
	250-499	More than adequate
	≥500	Excessive
Breast-feeding women#	<100	Insufficient
	≥100	Adequate

*Excludes pregnant or lactating women.
#Given that iodine requirements are increased in breast-feeding women (see The RDA), the numbers for median urinary excretion concentrations are lower than one would expect because iodine is also excreted in breast milk.

In many countries, serum TSH concentration is used in the screening for congenital hypothyroidism in newborns. Newborn TSH can be used as an indicator of population iodine status. Yet, in older children and adults, serum TSH is not a sensitive indicator of iodine status as concentrations are usually maintained within a normal range despite frank iodine deficiency (12). Serum thyroglobulin concentration in school-age children is a sensitive marker of iodine status in populations (13). In areas of endemic goiter, changes in thyroid size reflect long-term iodine nutrition (months to years). Assessment of the goiter rate in a population is used to define the severity of iodine deficiency, as well as to monitor the long-term impact of sustained salt iodization programs (4, 10). Finally, serum thyroid hormone concentrations do not adequately reflect iodine nutrition in populations (1).

Iodine deficiency disorders

All the adverse effects of iodine deficiency in animals and humans are collectively termed iodine deficiency disorders (reviewed in 1). Thyroid enlargement, or goiter, is one of the earliest and most visible signs of iodine deficiency. It is a physiologic adaptation of the thyroid gland in response to persistent stimulation by TSH (see Function). In mild iodine deficiency, thyroid enlargement may be enough to maximize the uptake of available iodine and provide the body with sufficient thyroid hormones. Yet, large goiters can obstruct the trachea and esophagus and damage the recurrent laryngeal nerves.

More severe cases of iodine deficiency result in impaired thyroid hormone synthesis known as hypothyroidism. Adequate iodine intake will generally reduce the size of goiters, but the reversibility of the effects of hypothyroidism depends on an individual's life stage. Iodine deficiency-induced hypothyroidism has adverse effects in all stages of development but is most damaging to the developing brain. In addition to regulating many aspects of growth and development, thyroid hormones are important for the migration, proliferation, and differentiation of specific neuronal populations, the overall architecture of the brain's cortex, the formation of axonal connections, and the myelination of the central nervous system, which occurs both before and shortly after birth (reviewed in 14).

The effects of iodine deficiency at different life stages are discussed below.

Pregnancy and lactation

Daily iodine requirements are significantly increased in pregnant and breast-feeding women because of (1) the increased thyroid hormone production and transfer to the fetus in early pregnancy before the fetal thyroid gland becomes functional, (2) iodine transfer to the fetus during late gestation, (3) increased urinary iodine excretion, and (4) iodine transfer to the infant via breast milk (see also The RDA) (12, 15).

During pregnancy, the size of the thyroid gland is increased by 10% in women residing in iodine-sufficient regions and increased by 20%-40% in those living in iodine-deficient regions (16). Iodine deficiency during pregnancy can result in hypothyroidism in women. Maternal hypothyroidism has been associated with increased risk for preeclampsia, miscarriage, stillbirth, preterm birth, and low-birth-weight infants (reviewed in 16). In addition, severe iodine deficiency during pregnancy may result in congenital hypothyroidism and neurocognitive deficits in the offspring (see Prenatal development) (12).

Iodine-deficient women who are breast-feeding may not be able to provide sufficient iodine to their infants who are particularly vulnerable to the effects of iodine deficiency (see Newborns and infants) (17). A daily prenatal supplement of 150 μg of iodine, as recommended by the American Thyroid Association (ATA) (16), will help to ensure that US pregnant and breast-feeding women consume sufficient iodine during these critical periods. In iodine-deficient areas where iodized salt is not available, the Iodine Global Network (IGN; formerly the International Council for the Control of Iodine Deficiency Disorders), the World Health Organization (WHO), and UNICEF recommend that lactating women receive a single annual dose of 400 mg of iodine (or 250 μg/day) and exclusively breast-feed for at least six months. When breast-feeding is not possible, direct supplementation of the infant (<2 years old) with a single annual dose of 200 mg of iodine (or 90 μg/day) is advised (4). A randomized and placebo-controlled trial recently demonstrated that maternal supplementation (with a single 400-mg dose of iodine) improved the iodine status of breast-fed infants more efficiently than direct infant supplementation (with a single 100 mg-dose of iodine) for a period of at least six months (18). Yet, supplementation of lactating women failed to increase maternal urinary iodine concentrations above 100 μg/L, suggesting that supplemented mothers remained deficient in iodine (18).

Prenatal development

Fetal iodine deficiency is caused by iodine deficiency in the mother (see Pregnancy and lactation). During pregnancy, before the fetal thyroid gland becomes functional at 16-20 weeks' gestation, maternal thyroxine (T_4) crosses the placenta to promote normal embryonic and fetal development. Hence, maternal iodine deficiency and hypothyroidism can result in adverse pregnancy complications, including fetal loss, placental abruption, preeclampsia, preterm delivery, and congenital hypothyroidism in the offspring (16). The effects of maternal hypothyroidism on the offspring depend on the timing and severity of *in utero* iodine deficiency. A severe form of congenital hypothyroidism may lead to cretinism, a condition associated with irreversible mental retardation. The clinical picture of neurological cretinism in the offspring includes severe mental and physical retardation, deafness, mutism, and motor spasticity.

A myxedematous form of cretinism has been associated with coexisting iodine and selenium deficiency in central Africa (see Nutrient interactions) and is characterized by a less severe degree of mental retardation than in neurological cretinism. Yet, affected individuals exhibit all the features of severe hypothyroidism, including severe growth retardation and delayed sexual maturation (12). Two longitudinal cohort studies (one in the UK and one in Australia) recently observed that even mild-to-moderate iodine deficiency during pregnancy was associated with reduced scores of IQ and various measures of literacy performance in children 8 to 9 years of age (19, 20).

Newborns and infants (up to one year of age)

Infant mortality is higher in areas of severe iodine deficiency than in iodine-replete regions, and several studies have demonstrated an increase in childhood survival upon correction of the iodine deficiency (8, 21, 22). Infancy is a period of rapid brain growth and development. Sufficient thyroid hormone, which depends on adequate iodine intake, is essential for normal brain development. Even in the absence of congenital hypothyroidism, iodine deficiency during infancy may result in abnormal brain development and, consequently, impaired intellectual development (23, 24).

Children and adolescents

Iodine deficiency in children and adolescents is often associated with goiter. The incidence of goiter peaks in adolescence and is more common in girls than boys. School-age children in iodine-deficient areas show poorer school performance, lower IQs, and a higher incidence of learning disabilities than matched groups from iodine-sufficient areas. Three meta-analyses of mainly cross-sectional studies concluded that chronic iodine deficiency was associated with reduced mean IQ scores by 7-13.5 points in participants (primarily children) (25-27). However, these observational studies did not distinguish between iodine deficiency during pregnancy and during childhood, and such observational studies may be confounded by social, economic, and educational factors that influence child development.

Adults

Inadequate iodine intake may also result in goiter and hypothyroidism in adults. Although the effects of hypothyroidism are more subtle in the brains of adults than children, research suggests that hypothyroidism results in poor social and economic achievements due to low educability, apathy, and reduced work productivity (28). Other symptoms of hypothyroidism in adults include fatigue, weight gain, cold intolerance, and constipation.

Finally, because iodine deficiency induces an increase in the iodine trapping capacity of the thyroid, iodine-deficient individuals of all ages are more susceptible to radiation-induced thyroid cancer (see Disease Prevention), as well as to iodine-induced hyperthyroidism after an increase in iodine intakes (see Safety) (2).

Individuals and populations at risk of iodine deficiency

While the risk of iodine deficiency for populations living in iodine-deficient areas without adequate iodine fortification programs is well recognized, concerns have been raised that certain subpopulations in countries considered iodine-sufficient may not consume adequate iodine (7, 29). The greater use of methods assessing iodine status (see Biomarkers of iodine status) has shown that iodine deficiency also occurs in areas where the prevalence of goiter is low, in coastal areas, in highly developed countries, and in regions where iodine deficiency was previously eliminated (4).

The US is currently considered to be iodine-sufficient. Yet, in recent years, dietary intakes of iodine in the US population have decreased. Data from the latest US National Health and Nutrition Examination Survey (NHANES 2009-2010) indicated that the median urinary iodine concentration for the general population was 144 μg/L compared to 164 μg/L reported in previous assessments (NHANES 2005-2006 and 2007-2008) (30, 31). In addition to regional differences across the US, ethnic variations have been found. In all age groups, median urinary iodine concentrations were shown to be lower in African Americans than in Hispanics and Caucasians.

In addition, median urinary iodine concentrations in nonpregnant women of childbearing age and pregnant women indicate that mild iodine deficiency has re-emerged in the US in recent years (31).

Nonpregnant women

Data from US NHANES 2007-2010 indicated that 37.3% of nonpregnant women (ages 15-44 years) had urinary iodine concentrations lower than 100 μg/L, reflecting potentially insufficient iodine intakes (see Biomarkers of iodine status) (31). Only one-fifth of nonpregnant women reported using iodine-containing supplements in an earlier NHANES (2001-2006) (32). Yet, adequate intakes of iodine in women of childbearing age (150 μg/day; see The RDA) are essential for optimum stores of iodine, especially if they are considering pregnancy. Some experts suggested a daily consumption of 250 μg of iodine before conception to ensure adequate thyroid hormone production and iodine supply to the embryo and fetus during pregnancy (see Pregnancy and lactation) (12).

Pregnant women

There are no statistics on the global burden of iodine deficiency in pregnant women, but national and regional data suggest that this group is especially vulnerable. Given the increased iodine requirements during pregnancy, the median urinary iodine concentration should be at least of 150 μg/L (see Biomarkers of iodine status). Pooled data from NHANES 2005-2010 reported that US pregnant women had a median urinary iodine concentration of 129 μg/L, and the lowest median concentration (109 μg/L) was observed during the first trimester of gestation, when the embryo/fetus relies exclusively on maternal thyroid hormones (31).

Breast-feeding women

While data regarding the iodine status of breast-feeding women in the US are limited, dietary intakes that were inadequate during pregnancy are likely to be insufficient in a significant fraction of breast-feeding women (33, 34). A systematic review of the literature recently reported suboptimal dietary iodine intakes in breast-feeding women in some countries with a mandatory fortification program, including Denmark, Australia, and India (35). The American Thyroid Association (ATA) recommends that all North American women who are pregnant or breast-feeding supplement their dietary iodine intake with 150 μg/day of iodine (36).

Breast-fed and weaning infants

The body of a healthy newborn contains only about 300 μg of iodine, which makes newborns extremely vulnerable to iodine deficiency (28), and breast-fed infants are entirely reliant on maternal iodine intakes for thyroid hormone synthesis. Even in areas covered by a salt iodization program, weaning infants are at high risk of iodine deficiency, especially if they are not receiving iodine-containing infant formula (17).

Individuals consuming special diets

Diets that exclude iodized salt, fish, and seaweed have been found to contain very little iodine (9). Individuals consuming branded weight-loss foods may also be at risk of inadequate intakes (37). A small US cross-sectional study in 78 vegetarians and 63 vegans reported median urinary iodine concentrations of 147 μg/L and 78.5 μg/L, respectively, suggesting inadequate iodine intakes among vegans (38). Two cases of goiter and/or hypothyroidism have also been recently reported in children following restrictive diets to control esophageal inflammation (eosinophilic esophagitis) (39) or allergies (40).

Patients requiring parenteral nutrition

Although iodine is usually not added to parenteral nutrition (PN) solutions, topical iodine-containing disinfectants and other adventitious sources provide substantial amounts of iodine to some PN patients such that the occurrence of iodine deficiency is unlikely. Yet, deficiency might occur, especially in preterm infants with limited body stores, if chlorhexidine-based antiseptics replace iodinated antiseptics (28, 41).

Nutrient interactions

Concurrent deficiencies in selenium, iron, or vitamin A may exacerbate the effects of iodine deficiency (reviewed in 42).

Selenium

While iodine is an essential component of thyroid hormones, the selenium-containing iodothyronine deiodinases (DIOs) are enzymes (or selenoenzymes) required for the conversion of T_4 to the biologically active thyroid hormone, T_3 (see the article on Selenium). DIO1 activity may also be involved in regulating iodine homeostasis (43). In addition, glutathione peroxidases are selenoenzymes that protect the thyroid gland from hydrogen peroxide-induced damage during thyroid hormone synthesis (44). A randomized, placebo-controlled study in 151 pregnant women at risk of developing autoimmune thyroid disease found that selenium supplementation (200 μg/day in the form of selenomethionine) at 12 weeks of gestation until 12 months' postpartum reduced the risk of thyroid dysfunction and permanent hypothyroidism (45). However, another trial (the Selenium in Pregnancy Intervention Trial) found no benefit of selenium supplementation (60 μg/day from 12-14 weeks of gestation to delivery) over placebo on circulating autoantibody concentrations in pregnant women mildly deficient in iodine (46).

The epidemiology of coexisting iodine and selenium deficiencies in central Africa has been linked to the prevalence of myxedematous cretinism, a severe form of congenital hypothyroidism accompanied by mental and physical retardation. Selenium deficiency may be only one of several undetermined factors that might exacerbate the detrimental effects of iodine deficiency (42). Besides, results from randomized controlled intervention trials have shown that correcting only the selenium deficiency may have a deleterious effect on thyroid hormone metabolism in school-age children with co-existing selenium and iodine deficiency (47, 48). Finally, selenium deficiency in rodents was found to have little impact on DIO activities as it appears that selenium is being supplied in priority for adequate synthesis of DIOs at the expense of other selenoenzymes (44).

Iron

Severe iron-deficiency anemia can impair thyroid metabolism in the following ways: (1) by altering the TSH response of the pituitary gland; (2) by reducing the activity of thyroid peroxidase that catalyzes the iodination of thyroglobulin for the production of thyroid hormones; and (3) in the liver by limiting the conversion of T_4 to T_3, increasing T_3 turnover, and decreasing T_3 binding to nuclear receptors (49). It is estimated that goiter and iron-deficiency anemia coexist in up to 25% of school-age children in west and north Africa (42). A randomized controlled study in iron-deficient children with goiter showed a greater reduction in thyroid size following the consumption of iodized salt together with 60 mg/day of iron four times per week compared to placebo (50). Additional interventions have confirmed that correcting iron-deficiency anemia improved the efficacy of iodine supplementation to mitigate thyroid disorders (reviewed in 42, 49).

Vitamin A

In north and west Africa, vitamin A deficiency and iodine deficiency-induced goiter may coexist in up to 50% of children. Vitamin A status, like other nutritional factors, appears to influence the response to iodine prophylaxis in iodine-deficient populations (51). Vitamin A deficiency in animal models was found to interfere with the pituitary-thyroid axis by (1) increasing the synthesis and secretion of thyroid-stimulating hormone (TSH) by the pituitary gland, (2) increasing the size of the thyroid gland, (3) reducing iodine uptake by the thyroid gland and impairing the synthesis and iodination of thyroglobulin, and (4) increasing circulating concentrations of thyroid hormones (reviewed in 52). A cross-sectional study of 138 children with concurrent vitamin A and iodine deficiencies found that the severity of vitamin A deficiency was associated with higher risk of goiter and higher concentrations of circulating TSH and thyroid hormones (51). These children received iodine-enriched salt together with vitamin A (200,000 IU at baseline and at 5 months) or a placebo in a randomized, double-blind, 10-month trial. Vitamin A supplementation significantly decreased TSH concentration and thyroid volume compared to placebo (51). In another trial, vitamin A supplementation alone (without iodine) to iodine-deficient children reduced the volume of the thyroid gland, as well as TSH and thyroglobulin concentrations (53). Yet, supplemental vitamin A had no additional effect on thyroid function/hormone metabolism when children were also given iodized oil.

Goitrogens

Some foods contain substances that interfere with iodine utilization or thyroid hormone production; these substances are called goitrogens. The occurrence of goiter in the Democratic Republic of Congo has been related to the consumption of cassava, which contains linamarin, a compound that is metabolized to thiocyanate and blocks thyroidal uptake of iodine (1). In iodine-deficient populations, tobacco smoking has been associated with an increased risk for goiter (54, 55). Cyanide in tobacco smoke is converted to thiocyanate in the liver, placing smokers with low iodine intake at risk of developing a goiter. Moreover, thiocyanate affects iodine transport into the lactating mammary gland, leading to low iodine concentrations in breast milk and impaired iodine supply to the neonates/infants of smoking mothers (2). Some species of millet, sweet potatoes, beans, and cruciferous vegetables (e.g., cabbage, broccoli, cauliflower, and Brussels sprouts) also contain goitrogens (1). Further, the soybean isoflavones, genistein and daidzein, have been found to inhibit thyroid hormone synthesis (56). Most of these goitrogens are not of clinical importance unless they are consumed in large amounts or there is coexisting iodine deficiency. Industrial pollutants, such as perchlorate (see Safety), resorcinol, and phthalic acid, may also be goitrogenic (1, 57).

The Recommended Dietary Allowance (RDA)

The RDA for iodine was reevaluated by the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) in 2001 (**Table 2**). The recommended amounts were calculated using several methods, including the measurement of iodine uptake in the thyroid glands of individuals with normal thyroid function (9). Similar recommendations have been made by several organizations, including the American Thyroid Association (ATA) (16, 58), the World Health Organization (WHO), the Iodine Global Network (IGN; formerly the International Council for the Control of Iodine Deficiency Disorders), and the United Nations Children's Fund (UNICEF) (4). Of note, the WHO, IGN, and UNICEF recommend daily intakes of 250 μg of iodine for both pregnant and breast-feeding women (4).

Table 2. Recommended Dietary Allowance (RDA) for Iodine

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	110 (AI)	110 (AI)
Infants	7-12 months	130 (AI)	130 (AI)
Children	1-3 years	90	90
Children	4-8 years	90	90
Children	9-13 years	120	120
Adolescents	14-18 years	150	150
Adults	19 years and older	150	150
Pregnancy	all ages	-	220
Breast-feeding	all ages	-	290

Disease Prevention

Radiation-induced thyroid cancer

Radioactive iodine, especially iodine 131 (^{131}I), may be released into the environment as a result of nuclear reactor accidents, such as the 1986 Chernobyl nuclear accident in Ukraine and the 2011 Fukushima Daiichi nuclear accident in Japan. Thyroid accumulation of radioactive iodine increases the risk of developing thyroid cancer, especially in children (59). The increased iodine trapping activity of the thyroid gland in iodine deficiency results in increased thyroid accumulation of radioactive iodine (^{131}I). Thus, iodine-deficient individuals are at increased risk of developing radiation-induced thyroid cancer because they will accumulate greater amounts of radioactive iodine. Potassium iodide administered in pharmacologic doses (up to 130 mg for adults) within 48 hours before or eight hours after radiation exposure from a nuclear reactor accident can significantly reduce thyroid uptake of ^{131}I and decrease the risk of radiation-induced thyroid cancer (60). The prompt and widespread use of potassium iodide prophylaxis in Poland after the 1986 Chernobyl nuclear reactor accident may explain the lack of a significant increase in childhood thyroid cancer compared to fallout areas where potassium iodide prophylaxis was not widely used (61). In the US, the Nuclear Regulatory Commission (NRC) requires that consideration be given to potassium iodide as a protective measure for the general public in the case of a major release of radioactivity from a nuclear power plant (62). See also the US FDA's Potassium Iodide Information.

Disease Treatment

Fibrocystic breast changes

Fibrocystic breast changes constitute a benign (non-cancerous) condition of the breasts, characterized by lumpiness and discomfort in one or both breasts. Cyst formation and fibrous changes in the appearance of breast tissue occur in at least 50% of premenopausal women and are not usually associated with an increased risk of breast cancer (63). The cause of fibrocystic changes is not known, but variations in hormonal stimulation during menstrual cycles may trigger changes in breast tissue (63).

A few observational studies also suggested an association between benign breast diseases (including but not limited to fibrocystic changes) and thyroid disorders. Recently, a small case-control study (166 cases vs. 72 controls) showed that the frequency of benign breast diseases was greater in women with nodular goiter (54.9%) or Hashimoto thyroiditis (47.4%) than in euthyroid controls (29.2%) (64). Conversely, the prevalence of anti-thyroid autoimmunity and hypothyroidism was found to be significantly higher in women with benign breast diseases compared to controls (65, 66). Interestingly, correcting hypothyroidism with supplemental T_4 was found to improve some of the benign breast disease symptoms, including breast pain (mastalgia) and nipple discharge (65).

In estrogen-treated rats, iodine deficiency leads to changes similar to those seen in fibrocystic breasts, while iodine repletion reverses those changes (67). An uncontrolled study of 233 women with fibrocystic changes found that treatment with aqueous molecular iodine (I_2) at a dose of 0.08 mg of I_2/kg of body weight daily over 6 to 18 months was associated with improvement in pain and other symptoms in over 70% of participants (68). About 10% of the study participants reported side effects that were described by the investigators as minor. A double-blind, placebo-controlled trial of aqueous molecular iodine (0.07-0.09 mg of I_2/kg of body weight daily for six months) in 56 women with fibrocystic changes found that 65% of the women taking molecular iodine reported improvement compared to 33% of those taking the placebo (68). A double-blind, placebo-controlled trial in 87 women with documented breast pain reported that molecular iodine (1.5, 3, or 6 mg/day) for six months improved overall pain (69). In this study, 38.5% of the women receiving 1.5 mg/day, 37.9% of those receiving 3 mg/day, and 51.7% of those receiving 6 mg/day reported at least a 50% reduction in self-assessed breast pain compared to 8.3% in the placebo group.

Large-scale, controlled clinical trials are needed to determine the therapeutic value of molecular iodine in fibrocystic breasts. Besides, the doses of iodine used in these studies (1.5 to 6 mg/day for a 60 kg person) are higher than the tolerable upper intake level (UL) recommended by the Food and Nutrition Board of the Institute of Medicine and should only be used under medical supervision (see Safety).

Sources

Food sources

Data from the ongoing US Total Diet Study, which monitors the levels of some contaminants and nutrients in food products, indicates that dietary iodine intakes in adults range between 138 and 268 micrograms (μg)/day. Considerably higher average intakes (304-353 μg/day of iodine) were reported for boys 14 to 16 years of age (70).

Seafood is rich in iodine because marine animals can concentrate the iodine from seawater. Certain types of edible seaweed (e.g., wakame) are also very rich in iodine (71). The iodine content of food that is grown or raised on a particular soil depends on the iodine content of this soil. In the US, dairy products contribute up to 90% of total estimated iodine intakes in infants, at least 70% in children (ages, 2-10 years), 53%-63% in adolescents (ages, 14-16 years), and about 50% in adults (70). In the UK and northern Europe, iodine levels in dairy products tend to be lower in summer when cattle are allowed to graze in pastures with low soil iodine content (9).

Other good sources of dietary iodine include eggs, fruit, grain products, and poultry (70). Processed foods can contribute to iodine intake if iodized salt or food additives, such as calcium iodate and potassium iodate, are added during production. Yet, in the US, virtually no iodized salt is used in the manufacturing of processed food and fast food products, and the food industry is not required to list the iodine content on food packaging (72). **Table 3** lists the iodine content of some iodine-rich foods in micrograms (μg). Because the iodine content of foods can vary considerably, these values should be considered approximate (73).

Table 3. Some Food Sources of Iodine

Food	Serving	Iodine (μg)
Salt (iodized)	1 gram	77
Cod	3 ounces*	99
Shrimp	3 ounces	35
Fish sticks	2 fish sticks	35
Tuna, canned in oil	3 ounces (½ can)	17
Milk (cow's)	1 cup (8 fluid ounces)	99
Egg, boiled	1 large	12
Navy beans, cooked	½ cup	32
Potato with peel, baked	1 medium	60
Turkey breast, baked	3 ounces	34
Seaweed	¼ ounce, dried	Variable; may be greater than 4,500 μg (4.5 mg)

*A three-ounce serving of meat is about the size of a deck of cards.

Supplements

Over-the-counter iodine supplements

Potassium iodide is available as a nutritional supplement, typically in combination products, such as multivitamin/mineral supplements. Iodine makes up approximately 77% of the total weight of potassium iodide (56). A multivitamin/mineral supplement that contains 100% of the daily value (DV) for iodine provides 150 μg of iodine. Although most people in the US consume sufficient iodine in their diets (see Sources), an additional 150 μg/day is unlikely to result in excessive iodine intake. The American Thyroid Association (ATA) recommends prenatal supplementation with 150 μg/day of iodine and advises against the ingestion of ≥500 μg/day of iodine from iodine, potassium iodine, and kelp supplements for children and adults, and during pregnancy and lactation (see also Safety) (36, 74).

Iodine fortification programs

The fortification of salt with iodine is a feasible and inexpensive method to eliminate iodine deficiency, and salt iodization programs have been implemented in almost all countries. In North America, salt fortification with iodine is mandated in Canada and some parts of Mexico, but only voluntary in the US such that only 52% of US table salt is iodized and only one-fifth of the total salt consumed in the US is iodized (72, 75). Potassium iodide (KI), cuprous iodide (CuI), and potassium iodate (KIO_3) are used to iodize salt. The US Food and Drug Administration (FDA) recommends between 46 and 76 μg of iodine per gram of salt in iodized salt. However, the recent analysis of 88 US iodized food-grade salt samples revealed that the iodine content was below the recommended range in 52% of the samples and above the range in 7% of the samples (76).

In other countries, salt commonly contains 20-50 μg of iodine per gram of salt, depending on local regulations (76). In countries like Denmark (77), Australia (78, 79), and New Zealand (80), the use of iodized salt in the bread-making process is mandated. Additional approaches have been explored, including sugar fortification (81), egg fortification (82), use of iodized salt in the preparation of fermented fish and fish sauce (83), and use of iodine-rich crop fertilizers (84). In addition, fortification of livestock feeds with iodine and the use of iodophors for sanitation during milking contribute to increasing iodine content in dairy products (85). Finally, annual doses of iodized vegetable oil are administered orally or intramuscularly to individuals in iodine-deficient populations who do not have access to iodized salt (4, 56).

Safety

Acute toxicity

Acute iodine poisoning is rare and usually occurs only with doses of many grams. Symptoms of acute iodine poisoning include burning of the mouth, throat, and stomach, fever, nausea, vomiting, diarrhea, a weak pulse, cyanosis, and coma (1).

Excessive iodine intakes

Risk of iodine-induced hyperthyroidism in iodine-deficient individuals

Iodine supplementation programs in iodine-deficient populations have been associated with an increased incidence of iodine-induced hyperthyroidism (IIH), especially in older people with multi-nodular goiter (86). Iodine intakes of 150-200 μg/day have been found to increase the incidence of IIH in iodine-deficient populations. Iodine deficiency increases the risk of developing autonomous thyroid nodules that are unresponsive to TSH control (see Function). These autonomous nodules may then overproduce thyroid hormones in response to sudden iodine supply. IIH symptoms include weight loss, tachycardia (high pulse rate), muscle weakness, and skin warmth. IIH can be dangerous in individuals with underlying heart disease. Yet, because the primary cause of nodular goiter and IIH is chronic iodine deficiency, the benefit of iodization programs largely outweighs the risk of IIH in iodine-deficient populations (1).

Risk of hypothyroidism in iodine-sufficient individuals

In iodine-sufficient individuals, excess iodine intake is most commonly associated with elevated blood concentrations of thyroid stimulating hormone (TSH) that inhibit thyroid hormone production, leading to hypothyroidism and goiter. A slightly elevated serum TSH concentration without a decrease in serum T_4 or T_3 is the earliest sign of abnormal thyroid function when iodine intake is excessive. In iodine-sufficient adults, elevated serum TSH has been found at chronic iodine intakes of ≥750 μg/day in children and ≥1,700 μg/day in adults. Because various edible seaweed species substantially contribute to traditional Asian meals, average Japanese dietary intakes are estimated to range between 1,000 and 3,000 μg of iodine/day (71). Iodine-induced goiter and hypothyroidism are not uncommon in Japan and can be reversed by restricting seaweed intake (71). Prolonged intakes of more than 18,000 μg/day (18 mg/day) increase the incidence of goiter in adults. In newborns, iodine-induced goiter and hypothyroidism can be due to either high maternal intakes or high exposure to iodized antiseptics (87). In order to minimize the risk of adverse health effects, the Food and Nutrition Board of the US Institute of Medicine set a tolerable upper intake level (UL) for iodine that is likely to be safe in almost all individuals. The UL values for iodine are listed in **Table 4** by age group; the UL does not apply to individuals who are being treated with iodine under medical supervision (74).

Table 4. Tolerable Upper Intake Level (UL) for Iodine

Age Group	UL (μg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	200
Children 4-8 years	300
Children 9-13 years	600
Adolescents 14-18 years	900
Adults 19 years and older	1,100

*Source of intake should be from food and formula only.

Individuals with increased sensitivity to excess iodine intake

Individuals with iodine deficiency and those with preexisting thyroid disease, including nodular goiter, autoimmune Hashimoto thyroiditis, Graves disease, and a history of partial thyroidectomy, may be sensitive to iodine intake levels considered safe for the general population and may not be protected by the UL for iodine (9). Infants, the elderly, and pregnant and lactating women may also be more susceptible to excess iodine (see Supplements) (74).

Do elevated and/or insufficient iodine intakes increase the risk of thyroid cancer?

Over the past decades, the incidence of thyroid cancer has increased worldwide. In the US, the incidence of thyroid cancer — representing 4% of all newly diagnosed cancers — has increased from 4.9 cases per persons in 1983 to 14.7 cases per 100,000 persons in 2011, but mortality rate from thyroid cancer has remained low (about 0.5 per 100,000 persons) (88). Accounting for over 80% of all thyroid cancers, thyroid papillary cancer is less aggressive and has a better prognosis than thyroid follicular cancer or anaplastic thyroid cancer. The increasing incidence of thyroid cancer worldwide is likely due at least in part to the improved screening and diagnosis activities. However, because it has coincided with the introduction of iodine fortification programs, a possible contribution of increased iodine intakes has been hypothesized. Yet, in the US, the increasing incidence of thyroid cancers (primarily papillary cancer) over the last few decades was paralleled with a reduction in average iodine intake (89).

Ecologic studies also suggested that iodine prophylaxis in populations that were previously iodine deficient was associated with an increased incidence of the papillary rather than the follicular cancer subtype, and with a reduced incidence of the more aggressive anaplastic thyroid cancer (89). While changes in iodine intakes appear to affect the histological type of thyroid cancer, it is not yet clear whether iodine deficiency and/or iodine excess increase the risk of thyroid cancer (88).

Drug interactions

Amiodarone, a medication used to prevent abnormal heart rhythms, contains high levels of iodine and may affect thyroid function (90, 91). Antithyroid drugs used to treat hyperthyroidism, such as propylthiouracil (PTU), methimazole, and carbimazole, may increase the risk of hypothyroidism. Additionally, the long-term use of lithium to treat mood disorders may increase the risk of hypothyroidism (92). Further, the use of pharmacologic doses of potassium iodide may decrease the anticoagulant effect of warfarin (coumarin) (56).

Contaminants

Perchlorate is an oxidizing agent found in rocket propellants, airbags, fireworks, herbicides, and fertilizer. Mainly as a result of human activity, perchlorate has been found to contaminate drinking water and many foods (57). Chronic exposure to perchlorate concentrations at levels greater than 20 μg per kg body weight (bw) per day interferes with iodine uptake by the thyroid gland and may lead to hypothyroidism (93). The US Environmental Protection Agency (EPA) recommends that daily oral exposure to perchlorate should not exceed 0.7 μg/kg bw to protect the most sensitive population, i.e., the fetuses of pregnant women who might be deficient in iodine and/or hypothyroid (94). Among all age groups, children aged two years have the highest estimated perchlorate intakes per day with 0.35-0.39 μg/kg bw/day. Average estimated intakes of perchlorate in US adults range between 0.08 and 0.11 μg/kg bw/day (70).

Linus Pauling Institute Recommendation

The RDA for iodine is sufficient to ensure normal thyroid function. There is presently no evidence that iodine intakes higher than the RDA are beneficial. Most people in the US consume sufficient iodine in their diets, making supplementation unnecessary.

Pregnant and breast-feeding women

Given the importance of sufficient iodine during prenatal development and infancy, pregnant and breast-feeding women should take a supplement that provides 150 μg of iodine per day (see Deficiency).

Older adults (>50 years)

Because aging has not been associated with significant changes in the requirement for iodine, the LPI recommendation for iodine intake is not different for older adults.

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Iron

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Summary

- Iron is an essential component of hundreds of proteins and enzymes that support essential biological functions, such as oxygen transport, energy production, and DNA synthesis. Hemoglobin, myoglobin, cytochromes, and peroxidases require iron-containing heme as a prosthetic group for their biological activities. *(More information)*
- Because the body excretes very little iron, iron metabolism is tightly regulated. In particular, the iron regulatory hormone, hepcidin, blocks dietary iron absorption, promotes cellular iron sequestration, and reduces iron bioavailability when body iron stores are sufficient to meet requirements. *(More information)*
- Iron status can be assessed in healthy men and nonpregnant women using laboratory tests that measure serum ferritin (iron-storage protein), serum iron, total iron binding capacity, saturation of transferrin (the main iron carrier in blood), and soluble transferrin receptor. *(More information)*
- Iron deficiency results from an inadequate supply of iron to cells following depletion of the body's reserves. Microcytic anemia occurs when body iron stores are so low that hemoglobin synthesis and red blood cell formation are severely impaired. *(More information)*
- Iron deficiency is the most common nutritional deficiency worldwide, affecting primarily children, women of childbearing age, pregnant women, frequent blood donors, and individuals with certain medical conditions. *(More information)*
- Much of our iron requirement is met through recycling iron from senescent red blood cells. The recommended dietary allowance (RDA) for iron is 8 mg/day for men and postmenopausal women, 18 mg/day for premenopausal women, and 27 mg/day for pregnant women. *(More information)*
- Iron deficiency with or without anemia in children has been associated with poor cognitive development, poor school achievement, and abnormal behavior patterns. Limited evidence suggests that iron supplementation has no effect on psychomotor development and cognitive function of anemic iron-deficient infants younger than three years but may improve attention and concentration in older children, adolescents, and women with anemia and/or iron deficiency. *(More information)*
- Heme iron comes from hemoglobin and myoglobin in animal food sources and represents 10%-15% of total dietary iron intake of meat eaters. Yet, because it is much better absorbed than nonheme iron found in both plant and animal food sources, heme iron contributes up to 40% of total absorbed iron. *(More information)*
- Toxic iron deposition in vital organs in patients affected by hereditary hemochromatosis has been associated with numerous chronic conditions, including liver cancer and type 2 diabetes mellitus. Increased heme iron intake and/or loss of iron homeostasis might also increase the risk of chronic disease in individuals free of genetic disorders. *(More information)*
- Iron supplementation may cause gastrointestinal irritation, nausea, vomiting, diarrhea, or constipation, and interfere with the absorption and efficacy of certain medications, including antibiotics and drugs used to treat osteoporosis, hypothyroidism, or Parkinson's disease symptoms. *(More information)*

Iron is the fourth most abundant element of Earth's crust and one of the best studied micronutrients in nutrition science (1, 2). It is a key element in the metabolism of all living organisms. Iron exists in two biologically relevant oxidation states: the ferrous form (Fe^{2+}) and the ferric form (Fe^{3+}). Iron is an essential component of hundreds of proteins and enzymes supporting essential biological functions, such as oxygen transport, energy production, DNA synthesis, and cell growth and replication.

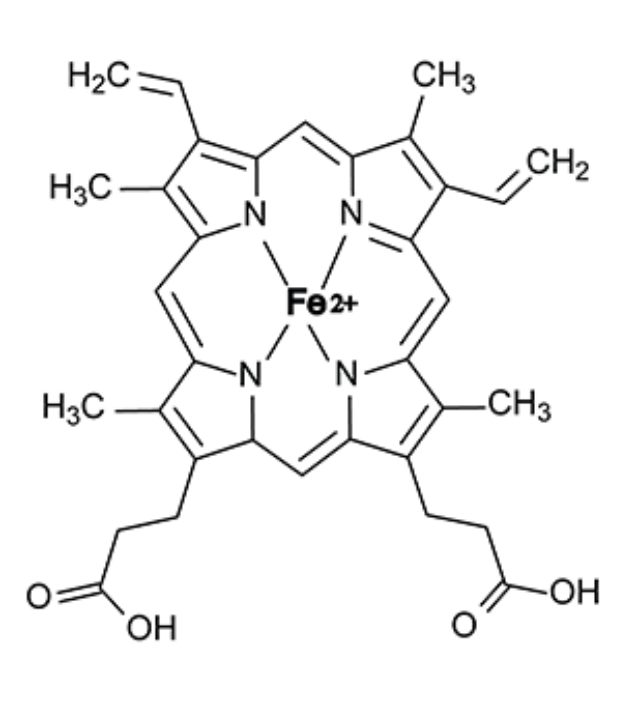
Function

Heme is an iron-containing compound found in a number of biologically important molecules (**Figure 1**). Some, but not all, iron-dependent proteins are heme-containing proteins (also called hemoproteins). Iron-dependent proteins that carry out a broad range of biological activities may be classified as follows (1, 3):

- Globin-heme: nonenzymatic proteins involved in oxygen transport and storage (e.g., hemoglobin, myoglobin, neuroglobin)
- Heme enzymes involved in electron transfer (e.g., cytochromes a, b, f; cytochrome c oxidase) and/or with oxidase activity (e.g., sulfite oxidase, cytochrome P450 oxidases, myeloperoxidase, peroxidases, catalase, endothelial nitric oxide synthase, cyclooxygenase)
- Iron-sulfur (Fe-S) cluster proteins with oxidoreductase activities involved in energy production (e.g., succinate dehydrogenase, isocitrate dehydrogenase, NADH dehydrogenase, aconitase, xanthine oxidase, ferredoxin-1) or involved in DNA replication and repair (DNA polymerases, DNA helicases)
- Nonheme enzymes that require iron as a cofactor for their catalytic activities (e.g., phenylalanine, tyrosine, tryptophan, and lysine hydroxylases; hypoxia-inducible factor (HIF) prolyl and asparaginyl hydroxylases; ribonucleotide reductase)
- Nonheme proteins responsible for iron transport and storage (e.g., ferritin, transferrin, haptoglobin, hemopexin, lactoferrin).

Iron-containing proteins support a number of functions, some of which are listed below.

Figure 1. Structure of Heme b



Oxygen transport and storage

Globin-hemes are heme-containing proteins that are involved in the transport and storage of oxygen and, to a lesser extent, may act as free radical scavengers (1). Hemoglobin is the primary protein found in red blood cells and represents about two-thirds of the body's iron (3). The vital role of hemoglobin in transporting oxygen from the lungs to the rest of the body is derived from its unique ability to acquire oxygen rapidly during the short time it spends in contact with the lungs and to release oxygen as needed during its circulation through the tissues. Myoglobin functions in the transport and short-term storage of oxygen in muscle cells, helping to match the supply of oxygen to the demand of working muscles (1). A third globin called neuroglobin is preferentially expressed in the central nervous system, but its function is not well understood (4).

Electron transport and energy metabolism

Cytochromes are heme-containing enzymes that have important roles in mitochondrial electron transport required for cellular energy production and thus life. Specifically, cytochromes serve as electron carriers during the synthesis of ATP, the primary energy storage compound in cells. Cytochrome P450 (CYP) is a family of enzymes involved in the metabolism of a number of important biological molecules (including organic acids; fatty acids; prostaglandins; steroids; sterols; and vitamins A, D, and K), as well as in the detoxification and metabolism of drugs and pollutants. Nonheme iron-containing enzymes in the citric acid cycle, such as NADH dehydrogenase and succinate dehydrogenase, are also critical to energy metabolism (1).

Antioxidant and beneficial pro-oxidant functions

Catalase and some peroxidases are heme-containing enzymes that protect cells against the accumulation of hydrogen peroxide, a potentially damaging reactive oxygen species (ROS), by catalyzing a reaction that converts hydrogen peroxide to water and oxygen. As part of the immune response, some white blood cells engulf bacteria and expose them to ROS in order to kill them. The synthesis of one such ROS, hypochlorous acid, by neutrophils is catalyzed by the heme-containing enzyme myeloperoxidase (1).

In addition, in the thyroid gland, heme-containing thyroid peroxidase catalyzes the iodination of thyroglobulin for the production of thyroid hormones such that thyroid metabolism can be impaired in iron deficiency and iron-deficiency anemia (see Nutrient Interactions).

Oxygen sensing

Inadequate oxygen (hypoxia), such as that experienced by those who live at high altitudes or those with chronic lung disease, induces compensatory physiologic responses, including increased red blood cell formation (erythropoiesis), increased blood vessel growth (angiogenesis), and increased production of enzymes utilized in anaerobic metabolism. Hypoxia is also observed in pathological conditions like ischemia/stroke and inflammatory disorders. Under hypoxic conditions, transcription factors known as hypoxia-inducible factors (HIF) bind to response elements in genes that encode various proteins involved in compensatory responses to hypoxia and increase their synthesis. Iron-dependent enzymes of the dioxygenase family, HIF prolyl hydroxylases and asparaginyl hydroxylase (factor inhibiting HIF-1 [FIH-1]), have been implicated in HIF regulation. When cellular oxygen tension is adequate, newly synthesized HIF-α subunits (HIF-1α, HIF-2α, HIF-3α) are modified by HIF prolyl hydroxylases in an iron/2-oxoglutarate-dependent process that targets HIF-α for rapid degradation. FIH-1-induced asparaginyl hydroxylation of HIF-α impairs the recruitment of co-activators to HIF-α transcriptional complex and therefore prevents HIF-α transcriptional activity. When cellular oxygen tension drops below a critical threshold, prolyl hydroxylase can no longer target HIF-α for degradation, allowing HIF-α to bind to HIF-1β and form a transcription complex that enters the nucleus and binds to specific hypoxia response elements (HRE) on target genes like the erythropoietin gene (*EPO*) (5).

DNA replication and repair

Ribonucleotide reductases (RNRs) are iron-dependent enzymes that catalyze the synthesis of deoxyribonucleotides required for DNA replication. RNRs also facilitate DNA repair in response to DNA damage. Other enzymes essential for DNA synthesis and repair, such as DNA polymerases and DNA helicases, are Fe-S cluster proteins. Although the underlying mechanisms are still unclear, depletion of intracellular iron was found to inhibit cell cycle progression, growth, and division. Inhibition of heme synthesis also induced cell cycle arrest in breast cancer cells (6).

Iron is required for a number of additional vital functions, including growth, reproduction, healing, and immune function.

Regulation

Systemic regulation of iron homeostasis

While iron is an essential mineral, it is potentially toxic because free iron inside the cell can lead to the generation of free radicals causing oxidative stress and cellular damage. Thus, it is important for the body to systemically regulate iron homeostasis. The body tightly regulates the transport of iron throughout various body compartments, such as developing red blood cells (erythroblasts), circulating macrophages, liver cells (hepatocytes) that store iron, and other tissues (7). Intracellular iron concentrations are regulated according to the body's iron needs (see below), but extracellular signals also regulate iron homeostasis in the body through the action of hepcidin.

Hepcidin, a peptide hormone primarily synthesized by liver cells, is the key regulator of systemic iron homeostasis. Hepcidin can induce the internalization and degradation of the iron-efflux protein, ferroportin-1; ferroportin-1 regulates the release of iron from certain cells, such as enterocytes, hepatocytes, and iron-recycling macrophages, into plasma (8). When body iron concentration is low and in situations of iron-deficiency anemia, hepcidin expression is minimal, allowing for iron absorption from the diet and iron mobilization from body stores. In contrast, when there are sufficient iron stores or in the case of iron overload, hepcidin inhibits dietary iron absorption, promotes cellular iron sequestration, and reduces iron bioavailability. Hepcidin expression is up-regulated in conditions of inflammation and endoplasmic reticulum stress and down-regulated in hypoxia (9). In Type 2B hemochromatosis, deficiency in hepcidin due to mutations in the hepcidin gene, *HAMP*, causes abnormal iron accumulation in tissues (see Iron Overload). Of note, hepcidin is also thought to have a major antimicrobial role in the innate immune response by limiting iron availability to invading microorganisms (see Iron withholding defense during infection) (10).

Regulation of intracellular iron

Iron-responsive elements (IREs) are short sequences of nucleotides found in the messenger RNAs (mRNAs) that code for key proteins in the regulation of iron storage, transport, and utilization. Iron regulatory proteins (IRPs: IRP-1, IRP-2) can bind to IREs and control mRNA stability and translation, thereby regulating the synthesis of specific proteins, such as ferritin (iron storage protein) and transferrin receptor-1 (TfR; controls cellular iron uptake) (1, 2).

When the iron supply is low, iron is not available for storage or release into plasma. Less iron binds to IRPs, allowing the binding of IRPs to IREs. The binding of IRPs to IREs located in the 5'end of mRNAs coding for ferritin and ferroportin-1 (iron efflux protein) inhibits mRNA translation and protein synthesis. Translation of mRNA that codes for the key regulatory enzyme of heme synthesis in immature red blood cells is also reduced to conserve iron. In contrast, IRP binding to IREs in the 3' end of mRNAs that code for TfR and divalent metal transporter-1 (DMT1) stimulates the synthesis of iron transporters, thereby increasing iron uptake into cells (1, 2).

When the iron supply is high, more iron binds to IRPs, thereby preventing the binding of IRPs to IREs on mRNAs. This allows for an increased synthesis of proteins involved in iron storage (ferritin) and efflux (ferroportin-1) and a decreased synthesis of iron transporters (TfR and DMT1) such that iron uptake is limited (2). In the brain, IRPs are also prevented from binding to the 5'end of amyloid precursor protein (APP) mRNA, allowing for APP expression. APP stimulates iron efflux from neurons through stabilizing ferroportin-1. In Parkinson's disease (PD), APP expression is inappropriately suppressed, leading to iron accumulation in dopaminergic neurons (11, 12).

Iron withholding defense during infection

Iron is required by most infectious agents to grow and spread, as well as by the infected host in order to mount an effective immune response. Sufficient iron is critical for the differentiation and proliferation of T lymphocytes and the generation of reactive oxygen species (ROS) required for killing pathogens (13). During infection and inflammation, hepcidin synthesis is up-regulated, serum iron concentrations decrease, and concentrations of ferritin (the iron storage protein) increase, supporting the idea that sequestering iron from pathogens is an important host defense mechanism (2).

Recycling of iron

Total body content of iron in adults is estimated to be 2.3 g in women and 3.8 g in men (2). The body excretes very little iron; basal losses, menstrual blood loss, and the need of iron for the synthesis of new tissue are compensated by the daily absorption of a small proportion of dietary iron (1 to 2 mg/day). Body iron is primarily found in red blood cells, which contain 3.5 mg of iron per g of hemoglobin. Senescent red blood cells are engulfed by macrophages in the spleen, and about 20 mg of iron can be recovered daily from heme recycling. The released iron is either deposited to the ferritin of spleen macrophages or exported by ferroportin-1 (iron efflux protein) to transferrin (the main iron carrier in blood) that delivers iron to other tissues. Iron recycling is very efficient, with about 35 mg being recycled daily (1).

Assessment of iron status

Measurements of iron stores, circulating iron, and hematological parameters may be used to assess the iron status of healthy people in the absence of inflammatory disorders, parasitic infection, and obesity. Commonly used iron status biomarkers include serum ferritin (iron-storage protein), serum iron, total iron binding capacity (TIBC), and saturation of transferrin (the main iron carrier in blood; TSAT). Soluble transferrin receptor (sTfR) is also an indicator of iron status when iron stores are depleted. In iron deficiency and iron-deficiency anemia, the abundance of cell surface-bound transferrin receptors that bind diferric transferrin is increased in order to maximize the uptake of available iron. Therefore, the concentration of sTfR generated by the cleavage of cell-bound transferrin receptors is increased in iron deficiency. Hematological markers, including hemoglobin concentration, mean corpuscular hemoglobin concentration, mean corpuscular volume of red blood cells, and reticulocyte hemoglobin content can help detect abnormality if anemia is present (9, 14).

Of note, serum ferritin is an acute-phase reactant protein that is up-regulated by inflammation. Importantly, serum hepcidin concentration is also increased by inflammation to limit iron availability to pathogens. Therefore, it is important to include inflammation markers (e.g., C-reactive protein, fibrinogen) when assessing iron status to rule out inflammation (14).

Nutrient Interactions

Vitamin A

Vitamin A deficiency often coexists with iron deficiency and may exacerbate iron-deficiency anemia by altering iron metabolism (15). Vitamin A supplementation has been shown to have beneficial effects on iron-deficiency anemia and improve iron nutritional status among children and pregnant women (15, 16). The combination of vitamin A and iron seems to reduce anemia more effectively than either supplemental iron or vitamin A alone (17). Vitamin A may facilitate the mobilization of iron from storage sites to developing red blood cells for incorporation into hemoglobin (15, 16). Moreover, studies in rats have shown that iron deficiency alters plasma and liver levels of vitamin A (18, 19).

Copper

Adequate copper nutritional status is necessary for normal iron metabolism and red blood cell formation. Anemia is a clinical sign of copper deficiency, and iron has been found to accumulate in the livers of copper-deficient animals, indicating that copper (via copper-containing ceruloplasmin) is required for iron transport to the bone marrow for red blood cell formation (20). The connection between copper availability and iron metabolism has also been established in humans; copper deficiency can lead to secondary ceruloplasmin deficiency and hepatic iron overload and/or cirrhosis (21). Oral copper supplementation restored normal ceruloplasmin levels and plasma ferroxidase activity and corrected the iron metabolism disorder in a copper-deficient subject (22). Moreover, infants fed a high-iron formula absorbed less copper than infants fed a low-iron formula, suggesting that high iron intakes may interfere with copper absorption in infants (23).

Zinc

Zinc is essential to maintain adequate erythropoiesis. When zinc deficiency coexists with iron deficiency, it may exacerbate iron-deficiency anemia (24). On the other hand, high doses of iron supplements, taken together with zinc supplements on an empty stomach, may inhibit the absorption of zinc. When taken with food, supplemental iron does not appear to inhibit zinc absorption. Iron-fortified foods have not been found to impair zinc absorption (25, 26).

Calcium

The presence of calcium decreases iron absorption from both nonheme (i.e., most supplements and food sources other than meat, poultry, and seafood) and heme sources (27). However, calcium supplementation up to 12 weeks has not been found to change iron nutritional status, probably due to a compensatory increase in iron absorption (28). Individuals taking iron supplements should take them two hours apart from calcium-rich food or supplements to maximize iron absorption.

Iodine

Severe iron-deficiency anemia can impair thyroid metabolism in the following ways: (1) by altering the thyroid-stimulating hormone response of the pituitary gland; (2) by reducing the activity of thyroid peroxidase that catalyzes the iodination of thyroglobulin for the production of thyroid hormones; and (3) in the liver by limiting the conversion of T_4 to T_3, increasing T_3 turnover, and decreasing T_3 binding to nuclear receptors (29). It is estimated that goiter and iron-deficiency anemia coexist in up to 25% of school-age children in west and north Africa (30). A randomized controlled study in iron-deficient children with goiter showed a greater reduction in thyroid size following the consumption of iodized salt together with 60 mg/day of iron four times per week compared to placebo (31). Additional interventions have confirmed that correcting iron-deficiency anemia improved the efficacy of iodine supplementation to mitigate thyroid disorders (reviewed in 29, 30).

Deficiency

Levels of iron deficiency

Iron deficiency is the most common nutrient deficiency in the US and the world. Levels of iron deficiency are listed below from least to most severe.

Storage iron depletion

Iron stores are depleted, but the functional iron supply is not limited.

Early functional iron deficiency

Before the development of frank anemia, the supply of functional iron to tissues, including bone marrow, is inadequate such as to impair erythropoiesis.

Iron-deficiency anemia

By definition, anemia is present when individual hemoglobin concentrations fall below two standard deviations of the distribution mean for hemoglobin in a healthy population of the same gender and age and living at the same altitude (32). In 2013, iron-deficiency anemia was the leading cause of years lived with disability in children and adolescents in the 50 most populous countries. The countries with the highest prevalence of iron-deficiency anemia in individuals younger than 19 years were Afghanistan (41%) and Yemen (39.8%); India contributed the largest number of cases of anemia (147.9 million). The prevalence in the US was estimated to be 19.3% with nearly 16 million cases of iron-deficiency anemia in children and adolescents (33).

Iron-deficiency anemia occurs when there is inadequate iron to support normal red blood cell formation. The anemia of iron deficiency is usually characterized as microcytic and hypochromic, i.e., red blood cells are measurably smaller than normal and their hemoglobin content is decreased such that they are paler than normal. At this stage of iron deficiency, symptoms may be a result of inadequate oxygen delivery due to anemia and/or suboptimal function of iron-dependent enzymes. Changes in hematological parameters are used in the clinical diagnosis of iron-deficiency anemia (see Assessment of iron status). It is important to remember that iron deficiency is not the only cause of anemia, and that the diagnosis or treatment of iron deficiency solely on the basis of anemia may lead to misdiagnosis or inappropriate treatment of the underlying cause (34). See also the articles on Folate and Vitamin B_{12} for information on other nutritional causes of anemia.

Symptoms of iron deficiency

Most of the symptoms of iron deficiency are a result of the associated anemia and may include fatigue, rapid heart rate, palpitations, and rapid breathing on exertion. Iron deficiency impairs athletic performance and physical work capacity in several ways. In iron-deficiency anemia, the reduced hemoglobin content of red blood cells results in decreased oxygen delivery to active tissues. Decreased myoglobin levels in muscle cells limit the amount of oxygen that can be delivered to mitochondria for oxidative metabolism. Iron depletion also decreases the oxidative capacity of muscle by diminishing the mitochondrial content of cytochromes and other iron-dependent enzymes required for electron transport and ATP synthesis (see Function) (35).

Poor thyroid function and impaired thyroid hormone synthesis likely disrupt the ability to maintain a normal body temperature on exposure to cold in iron-deficient individuals (see Function). Iron deficiency may also impair neutrophil phagocytosis and microbicidal activity and T-lymphocyte proliferative responses to infection (1). Severe iron-deficiency anemia may result in brittle and spoon-shaped nails, sores at the corners of the mouth, taste bud atrophy, and a sore tongue. In rare cases, advanced iron-deficiency anemia may cause difficulty in swallowing due to the formation of webs of tissue in the throat and esophagus due to a degradation of the pharyngeal muscles (36). The development of esophageal webs, also known as Plummer-Vinson syndrome, may require a genetic predisposition in addition to iron deficiency. Iron deficiency and iron-deficiency anemia in early childhood have been shown to impair psychomotor development and induce short- and long-term behavioral and cognitive alterations (reviewed in 37). Further, pica, a behavioral disturbance characterized by the consumption of non-food items, may be a symptom and a cause of iron deficiency (38).

Individuals at increased risk of iron deficiency

Life stage groups with increased requirements

Neonates and infants up to six months of age: Inadequate maternal iron body stores and anemia during pregnancy may reduce the duration of gestation and birth weight; preterm and/or low body-weight newborns are at increased risk of iron-deficiency anemia (14). Pregnancy complications, including preeclampsia and gestational diabetes mellitus, may also lead to low iron stores in preterm and term infants (14).

Most of the 150 to 250 mg of iron present in a full-term healthy newborn is accumulated during the third trimester of pregnancy and is sufficient for the first four to six months of life (34). Iron stores are essential for infants less than six months of age because breast milk is relatively poor in iron (0.2 mg/L-0.4 mg/L), and intestinal absorption of iron remains low until six months of age. High iron requirements during this period of sustained and rapid growth rate can worsen the deficit in body iron in preterm infants (14). Moreover, a review of randomized controlled trials suggested that infants with an early umbilical cord clamping (≤1 min after birth) are at least twice more likely to be iron-deficient at three to six months compared to those with delayed cord clamping (39). Yet, healthy full-term infants have little need for external sources of iron before six months of age (1).

Infants and children between the ages of 6 months and 3 years: A full-term infant's iron stores are usually sufficient to last for the early months of life, but there is an increased risk of iron deficiency for infants older than six months (1). Given the sustained need of iron for increasing tissue mass, blood volume, and replenishing iron stores, the recommended dietary allowance (RDA) for iron is 11 mg/day for infants aged seven to 12 months, as established by the US Institute of Medicine (see **Table 1**).

The RDA for iron is 7 mg/day for toddlers aged 1 to 3 years old. Based on the US National Health and Nutrition Examination Survey (NHANES) 1999-2002 data, the prevalence of iron deficiency in toddlers aged 12 to 35 months varies from 6.6%-15.2%, and the prevalence of iron-deficiency anemia is 0.9%-4.4%, depending on ethnicity and socioeconomic status (14).

Of note, the World Health Organization (WHO) and the American Academy of Pediatrics recommend universal screening for anemia at one year of age. Yet, a recent report by the US Preventive Services Task Force (USPSTF) stated there was insufficient evidence to assess the benefits versus harms of screening (34, 40).

Adolescents: Early adolescence is period of rapid growth. Blood loss that occurs with menstruation in adolescent girls adds to the increased iron requirement of adolescence (1). The RDA of iron is 11 mg/day and 15 mg/day for adolescent boys and girls, respectively (see **Table 1**).

Nonpregnant women of childbearing age: Based on data from NHANES 2003-2006, the percentage of US women with two out of three markers of iron status (i.e., hemoglobin, ferritin, and % transferrin saturation) below cutoff values for deficiency was 9.8% in nonpregnant women (41).

The use of oral contraceptives decreases menstrual blood losses and is thus associated with improved iron status compared to intrauterine devices (copper coil) (1).

Breast-feeding is associated with lower dietary iron needs, allowing for the repletion of iron stores depleted during pregnancy and delivery. However, iron repletion may be incomplete in high-parity women who are therefore at increased risk of iron deficiency (41).

Pregnant women: The requirement for iron is significantly increased during pregnancy due to increased iron utilization by the developing fetus and placenta, as well as maternal blood volume expansion (42). Analysis of data from NHANES 2005-2006 found that 18.1% of pregnant women (mean age, 27.5 years) were deficient in iron, as assessed by the log ratio of soluble transferrin receptor to serum ferritin (43). The prevalence of iron deficiency was greater during the second (20.7%) and third (29.7%) trimesters compared to the first trimester (4.5%) of gestation. Further, iron deficiency in pregnancy was found to be more prevalent in Mexican (23.6%) and Black Americans (29.6%) than in non-Hispanic White Americans (13.9%) (43).

Individuals with chronic blood losses

Chronic bleeding or acute blood loss may result in iron deficiency. One milliliter (mL) of blood with a hemoglobin concentration of 150 g/L contains 0.5 mg of iron. Thus, chronic loss of very small amounts of blood may result in iron deficiency.

Parasitic infestation: A common cause of chronic blood loss and iron deficiency in developing countries is intestinal parasitic infection (44).

Frequent blood donation: Individuals who donate blood frequently, especially menstruating women, may need to increase their iron intake to prevent deficiency because each 500 mL of blood donated contains between 200 and 250 mg of iron (45, 46).

Regular intense exercise: Daily iron losses have been found to be greater in athletes involved in intense endurance training. This may be due to expanding blood cell mass and muscle mass, increased microscopic bleeding from the gastrointestinal tract (with the regular use of anti-inflammatory drugs), or increased fragility and hemolysis of red blood cells (47). The Food and Nutrition Board estimates that the average requirement for iron may be 30% higher for those who engage in regular intense exercise (25).

Individuals with decreased iron absorption

Celiac disease: Celiac disease (celiac sprue) is an autoimmune disorder estimated to occur in 1% of the population. When people with celiac disease consume food or products that contain gluten, the immune system response damages the intestinal mucosa, which may result in nutrient malabsorption and iron-deficiency anemia (48).

Atrophic gastritis: This condition is usually associated with the presence of antibodies directed towards stomach cells and has been implicated in pernicious anemia (see the article on Vitamin B_{12}). Atrophic gastritis simultaneously impairs the absorption of both vitamin B_{12} and iron; yet, in menstruating women, iron deficiency may occur years before the depletion of vitamin B_{12} body stores (47).

***Helicobacter pylori* infection**: *H. pylori* infection is associated with iron-deficiency anemia, especially in children, even in the absence of gastrointestinal bleeding. Data from NHANES 2000-2001 in individuals older than three years showed that the presence of iron deficiency (based on serum ferritin concentrations) was 40% more prevalent in those infected with *H. pylori* than in *H. pylori*-free individuals (49). Occult gastrointestinal bleeding and competition for dietary iron by bacteria may explain iron deficiency in infected individuals. Moreover, *Helicobacter pylori* infection may also play a role in the pathogenesis of atrophic gastritis (47).

Inflammatory bowel diseases (IBD): Iron-deficiency anemia is commonly reported among patients with IBD (e.g., ulcerative colitis, Crohn's disease), likely due to both impaired intestinal absorption of iron and blood loss from ulcerated mucosa (50).

Gastric bypass surgery: Some types of gastric bypass (bariatric) surgery increase the risk of iron deficiency by causing malabsorption of iron, among other nutrients (51).

Obesity: An inverse association between body weight and iron status has been reported in several observational studies in children and adults (52, 53). Higher hepcidin expression in obese people may impair iron absorption despite adequate dietary intake of iron. Weight loss might lower serum hepcidin concentration and improve iron status in obese individuals (9).

Anemia of chronic disease: Acute and chronic inflammation may lead to abnormally low circulating concentrations of iron and to the development of anemia. This type of anemia of inflammation, also known as anemia of chronic disease (ACD), is commonly observed in inflammatory disorders, cancer, critical illness, trauma, chronic infection, and parasitic infestation. It is thought that anemia develops because dietary iron absorption and iron mobilization from body stores are inhibited by inflammation-induced hepcidin up-regulation (see also Systemic regulation of iron homeostasis) (9).

Other causes of iron deficiency

Vegetarian diet with inadequate sources of iron: Because iron from plants (nonheme iron) is less efficiently absorbed than that from animal sources (see Sources), the US Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) estimated that the bioavailability of iron from a vegetarian diet was only 10% versus 18% from a mixed Western diet. Therefore, the recommended dietary allowance (RDA) of iron for individuals consuming a completely vegetarian diet may be 1.8 times higher than the RDA for non-vegetarians (25). Yet, a vegetarian diet does not appear to be associated with an increased risk of iron deficiency when it includes whole grains, legumes, nuts, seeds, dried fruit, iron-fortified cereal, and green leafy vegetables (see Sources) (54).

Chronic kidney disease (CKD): Iron losses in CKD patients are due to significant gastrointestinal blood loss (1.2 L blood loss/year corresponding to ~400 mg iron/year) compared to individuals with normal kidney function (0.83 mL blood loss/day corresponding to ~100 mg iron/year). Estimated blood losses are even larger in patients on hemodialysis, and iron losses may be 1,000 to 2,000 mg/year or higher. Persistent inflammation in CKD patients may also contribute to inadequate iron supply for red blood cell formation despite adequate body iron stores (55).

The Recommended Dietary Allowance (RDA)

The RDA for iron was revised in 2001 and is based on the prevention of iron deficiency and maintenance of adequate iron stores in individuals eating a mixed diet (**Table 1**; 25).

Table 1. Recommended Dietary Allowance (RDA) for Iron

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.27 (AI)	0.27 (AI)
Infants	7-12 months	11	11
Children	1-3 years	7	7
Children	4-8 years	10	10
Children	9-13 years	8	8
Adolescents	14-18 years	11	15
Adults	19-50 years	8	18
Adults	51 years and older	8	8
Pregnancy	all ages	-	27
Breast-feeding	18 years and younger	-	10
Breast-feeding	19 years and older	-	9

Disease Prevention

Prevention or alleviation of iron deficiency or iron-deficiency anemia can limit the impact of iron inadequacy and defective erythropoiesis on the following health conditions and diseases.

Impaired psychomotor, cognitive, and intellectual development in children

Iron is critical for the development of the central nervous system, and iron deficiency is thought to be especially detrimental during the prenatal and early postnatal periods. Iron-dependent enzymes are required for nerve myelination, neurotransmitter synthesis, and normal neuronal energy metabolism (56). Most observational studies have found relationships between iron deficiency — with or without anemia — in children and poor cognitive development, poor school achievement, and abnormal behavior patterns (reviewed in 37). Whether psychomotor and mental deficits may be attributed to the lack of iron, only, or to a combination effect of iron deficiency and low hemoglobin concentrations — like in iron-deficiency anemia and anemia of inflammation — in early childhood remains unclear (14).

A recent systematic review of six small placebo-controlled trials (published between 1978 and 1989) in children with iron-deficiency anemia younger than 27 months found no convincing evidence that iron therapy (for less than 11 days) had any consistent effect on measures of psychomotor and mental development within 30 days of treatment initiation (57). Only one randomized, double-blind trial in anemic, iron-deficient infants examined the impact of iron therapy for four months and found a significant benefit on indices of cognitive development that needs to be further confirmed (58). A review of five randomized controlled trials in non-anemic, iron-deficient infants (0-9 months old) suggested an improvement in psychomotor (but not mental) development throughout the first 18 months of life (59). Iron supplementation in early infancy (4 to 6 months) also failed to demonstrate any long-term effect on cognitive performance and school performance at the age of 9 years compared to placebo (60). At present, evidence supporting any benefits of iron therapy on neurodevelopment outcomes in infants with iron deficiency, with or without anemia, remains limited.

Iron therapy might be more effective at improving cognitive outcomes in older children with anemia and/or iron deficiency. A systematic review of 17 randomized controlled trials found that iron supplementation had no effect on mental development of children under the age of 27 months but modestly improved scores of mental development in children over seven years of age (61). A more recent meta-analysis of randomized controlled trials in children older than six years, adolescents, and women with iron deficiency, anemia, or iron-deficiency anemia suggested that supplemental iron could improve attention and concentration irrespective of participants' iron status (62). A potential improvement in IQ measures with iron therapy was also reported in anemic participants regardless of their iron status. No additional benefits were observed regarding measures of memory performance, psychomotor function, and school achievements.

Alterations in brain functions due to iron deficiency are likely to be resistant to iron therapy when they occur in early childhood. Long-term consequences of early life iron deficiency may include poor socioeconomic achievements and increased risk of certain psychopathologies, including anxiety, depression, and schizophrenia (56).

Adverse pregnancy outcomes

Epidemiological studies provide strong evidence of an association between severe anemia in pregnant women and adverse pregnancy outcomes, such as low birth weight, preterm birth, and neonatal and maternal mortality (63). Although iron deficiency can be a major contributing factor to severe anemia, evidence that iron-deficiency anemia causes poor pregnancy outcomes is still lacking. In addition, iron supplementation during pregnancy was shown to improve iron status and hematological parameters in women but failed to significantly reduce adverse pregnancy outcomes, including low birth weight and/or prematurity, neonatal death, and congenital anomalies (64). Moreover, routine supplementation during pregnancy had no effect on the length of gestation or newborn Apgar scores (40). Nevertheless, most experts consider the control of maternal anemia to be an important part of prenatal health care, and the IOM recommends screening for anemia in each trimester of pregnancy (65).

The requirement for iron is greatly increased in the second and third trimesters, and the RDA for pregnant women is 27 mg/day of iron (see The Recommended Dietary Allowance) (25). The American College of Obstetricians and Gynecologists recommend screening all pregnant women for anemia and advise iron supplementation when required (66). Nonetheless, the US Preventive Services Task Force (40) and the American Academy of Family Physicians (67) consider that evidence is lacking to evaluate the harms and benefits of screening for iron-deficiency anemia and supplementing with iron during pregnancy.

In malaria-endemic regions, however, iron supplementation may improve pregnancy outcomes when provided in conjunction with measures of prevention and management of malaria. Two recent randomized, placebo-controlled trials failed to find an increased risk of malaria infection in both iron-deficient and iron-replete pregnant women supplemented with iron, supporting the use of universal iron supplementation in malaria-endemic countries that adopt malaria intermittent preventive treatment (IPT) (68, 69).

Lead toxicity

Children who are chronically exposed to lead, even in small amounts, are more likely to develop learning disabilities, behavioral problems, and have low IQs. Deficits in growth and neurologic development may occur in the infants of women exposed to lead during pregnancy and lactation. In adults, lead toxicity may result in kidney damage and high blood pressure. Although the use of lead in paint products, gasoline, and food cans has been discontinued in the US, lead toxicity continues to be a significant health problem, especially in children living in inner cities (70). In 2012, the US Centers for Disease Control and Prevention set the reference value for blood lead concentration at 5 micrograms per deciliter (μg/dL) to identify children at risk. Yet, there is no known blood lead concentration below which children are 100% safe (71).

Iron deficiency and lead poisoning share a number of the same risk factors, including low socioeconomic status, ethnic minority groups, and residence in urban areas. Iron deficiency may increase the risk of lead poisoning in children, especially by increasing the intestinal absorption of lead via the DMT1 intestinal transporter (72). However, the use of iron supplementation in lead poisoning might be reserved for children who are truly iron deficient or for iron-replete children with chronic lead exposure (e.g., living in lead-exposed housing) (72).

Disease Treatment

Restless legs syndrome

Restless legs syndrome (RLS; also called Willis-Ekbom disease) is a neurologic movement disorder of unknown etiology. People with RLS experience unpleasant sensations resulting in an irresistible urge to move their legs and transient relief with movement. These sensations are more common at rest and often interfere with sleep (73). The prevalence of RLS is higher in women than in men and increases with age (74). This syndrome appears to be inherited in about 50% of patients but has also been related to chronic kidney failure (73). Iron deficiency may be involved in RLS development, possibly by affecting the activity of tyrosine hydroxylase, a rate limiting iron-dependent enzyme in the synthesis of the neurotransmitter, dopamine (74). The management of RLS includes iron therapy and the use of drugs like dopamine agonists (73). Current clinical evidence is insufficient to evaluate whether iron therapy may help relieve some RLS symptoms (74). Yet, the Medical Advisory Board of the Willis-Ekbom Disease Syndrome Foundation suggests that iron status should be assessed in all patients with RLS, and iron therapy be attempted on a case-by-case basis in those who might benefit from it (73).

Sources

Food sources

The amount of iron in food or supplements that is absorbed and used by the body is influenced by the iron nutritional status of the individual and whether or not the iron is in the form of heme. Because it is absorbed by a different mechanism than nonheme iron, heme iron is more readily absorbed and its absorption is less affected by other dietary factors (2). In an attempt to improve body iron status, iron absorption is enhanced in individuals who are anemic or iron deficient compared to iron-replete individuals.

Heme iron

Heme iron comes mainly from hemoglobin and myoglobin in meat, poultry, and fish. Although heme iron accounts for only 10%-15% of the iron found in the diet, it may provide up to one-third of total absorbed dietary iron (54). The absorption of heme iron is less influenced by other dietary factors than that of nonheme iron (27).

Nonheme iron

Plants, dairy products, meat, and iron salts added to food and supplements are all sources of nonheme iron. The absorption of nonheme iron is strongly influenced by enhancers and inhibitors present in the same meal (27).

Enhancers of nonheme iron absorption

- **Vitamin C (ascorbic acid)**: Vitamin C strongly enhances the absorption of nonheme iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) and forming an absorbable, iron-ascorbic acid complex (75).
- **Other organic acids**: Citric, malic, tartaric, and lactic acids have some enhancing effects on nonheme iron absorption (1).
- **Meat, poultry, and fish**: Aside from providing highly absorbable heme iron, meat, fish, and poultry also enhance nonheme iron absorption. The mechanism for this enhancement of nonheme iron absorption is not clear (1, 25).

Inhibitors of nonheme iron absorption

- **Phytic acid (phytate)**: Phytic acid, present in legumes, whole grains, nuts, and seeds, inhibits nonheme iron absorption, probably by binding to it. Small amounts of phytic acid (5 to 10 mg) can reduce nonheme iron absorption by 50%. The absorption of iron from legumes, such as soybeans, black beans, lentils, mung beans, and split peas, has been shown to be as low as 2% (25). Food preparation, including soaking, germination, fermentation, and cooking, can help remove or degrade phytic acid (27).
- **Polyphenolic compounds**: Polyphenolic compounds in coffee, black tea, and herbal tea can markedly inhibit the absorption of nonheme iron (76). This effect may be reduced by the presence of vitamin C (27, 77).
- **Soy protein**: Soy protein, such as that found in tofu, has an inhibitory effect on iron absorption that is only partly related to its phytic acid content (27, 77).
- **Calcium**: Calcium appears to affect iron absorption from both heme and nonheme sources. Yet, its effect appears to be limited when one consumes a wide variety of food with varied levels of enhancers and inhibitors of iron absorption (27).

National surveys in the US have indicated that the average dietary intake of iron is 16 to 18 mg/day in men, 12 mg/day in pre- and postmenopausal women, and about 15 mg/day in pregnant women (25). Thus, the majority of premenopausal and pregnant women in the US consume less than the RDA for iron, and many men consume more than the RDA (see The Recommended Dietary Allowance). In the US, most grain products are fortified with nonheme iron. The iron content of some relatively iron-rich foods is listed in milligrams (mg) in **Table 2**. For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Iron

Food	Serving	Iron (mg)
Beef	3 ounces*	1.6
Chicken, liver, cooked, pan-fried	1 ounce	3.6
Oysters, Pacific, cooked	6 medium	13.8
Oysters, Eastern, cooked	6 medium	3.9
Clams, cooked, steamed	3 ounces	2.4
Tuna, light, canned in water	3 ounces	1.3

Mussels, cooked, steamed	3 ounces	5.7
Raisin bran cereal	1 cup	5.8-18.0
Raisins, seedless	1 small box (1.5 ounces)	0.8
Prune juice	6 fluid ounces	2.3
Prunes (dried plums)	~5 prunes (1.7 ounces)	0.4
Potato, with skin, baked	1 medium potato	1.8
Quinoa, cooked	½ cup	1.4
Spinach, cooked	1 cup	6.4
Swiss chard, cooked, boiled	½ cup	2.0
Beans, white, cooked	½ cup	3.3
Lentils, cooked	½ cup	3.3
Tofu, regular, raw	½ cup	6.6
Hazelnuts, dry-roasted	1 ounce	1.3
Cashews	1 ounce	1.9
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

Iron supplements are indicated for the prevention and treatment of iron deficiency and iron deficiency anemia. Individuals who are not at risk of iron deficiency (e.g., adult men and postmenopausal women) should not take iron supplements without an appropriate medical evaluation. A number of iron supplements are available, and different forms provide different proportions of elemental iron. Ferrous sulfate heptahydrate is 20% elemental iron, ferrous sulfate monohydrate is 33% elemental iron, ferrous gluconate is 12% elemental iron, and ferrous fumarate is 33% elemental iron. If not stated otherwise, the iron discussed in this article is elemental iron.

Iron Overload

Deregulation of intestinal iron absorption will result in iron overload because the body cannot excrete excess iron (2). However, iron overload due to prolonged iron supplementation is very rare in healthy individuals without a genetic predisposition. Several genetic disorders may lead to pathological accumulation of iron in the body despite normal iron intake. Supplementation of individuals who are not iron deficient should be avoided due to the frequency of undetected inherited diseases and recent concerns about the more subtle effects of chronic excess iron intake (see Diseases associated with iron overload).

Inherited iron-overload diseases

Hereditary hemochromatosis

Hereditary hemochromatosis (HH) refers to late-onset, autosomal recessive disorders of iron metabolism that result in iron accumulation in the liver, heart, and other tissues. Disorders may lead to cirrhosis of the liver, diabetes mellitus, cardiomyopathy (heart muscle damage), hypogonadism, arthropathy (joint problems), and increased skin pigmentation (reviewed in 78). There are four main types of HH, which are classified according to the specific gene that is mutated. The most common type of HH, called Type 1 or *HFE*-related HH, results from mutations in the *HFE* gene (79, 80). The majority of Type 1 HH cases are homozygous for mutation C282Y G>A (rs1800560) in the *HFE* gene. Another mutation found in 4% of patients with Type 1 HH is H63D C>G (rs1799945) in the *HFE* gene. The protein encoded by the *HFE* gene is thought to play a role in regulating intestinal absorption of dietary iron and with sensing the body's iron stores (81). *HFE* gene mutations are associated with an increased cellular uptake of iron. With a typical disease onset before age 30, juvenile hemochromatosis (HH Type 2) is much rarer than Type 1 HH and results from genetic mutations affecting either hemojuvelin (Type 2A) or hepcidin (Type 2B) function (82). HH Type 3 results from mutations in the transferrin receptor 2 gene (*TFR2*), and HH Type 4 (also called Ferroportin disease) results from mutations in the gene encoding ferroportin-1 (*SLC40A1*), a protein important in the export of iron from cells (see Regulation). Type 4 HH is the second most common inherited iron overload disorder after Type 1 HH (78).

Iron overload in HH is treated by phlebotomy, the removal of 500 mL of blood at a time, at intervals determined by the severity of the iron overload. Chelation therapy is an alternate option to deplete iron in HH patients who cannot undergo phlebotomy treatment. Individuals with HH are advised to avoid supplemental iron, but generally not told to avoid iron-rich food. High-dose vitamin C regimens may worsen iron overload in patients with HH (75). Alcohol consumption is strongly discouraged due to the increased risk of cirrhosis of the liver (83). Genetic testing, which requires a blood sample, is available for those who may be at risk for HH, for example, individuals with a family history of hemochromatosis.

Other inherited conditions

Other genetic disorders leading to iron overload include aceruloplasminemia, hypotransferrinemia, Friedreich's ataxia, and porphyria cutanea tarda (2).

Acquired iron-overload diseases

Iron overload may develop in individuals with severe hereditary anemias that are not caused by iron deficiency. Excessive dietary absorption of iron may occur in response to the body's continued efforts to form red blood cells. Beta-thalassemia is characterized by defective hemoglobin A synthesis due to mutations in the β-globin gene. Patients affected by thalassemia intermedia do not require blood transfusion as do those affected by the most severe form of the disease (called thalassemia major), yet they develop iron overload due to increased intestinal iron absorption (84). Other anemic patients at risk of iron overload include those with sideroblastic anemia, hemolytic anemia, pyruvate kinase deficiency, and thalassemia major, especially because they are treated with numerous transfusions. Patients with hereditary spherocytosis and thalassemia minor do not usually develop iron overload unless they are misdiagnosed as having iron deficiency and treated with large doses of iron over many years. Iron overload has also been associated with hemodialysis and chronic liver diseases (metabolic, viral, and alcoholic) (2).

Diseases associated with iron overload

Toxic iron deposition in vital organs in hereditary hemochromatosis (HH) has been associated with an increased incidence of liver cancer, type 2 diabetes mellitus, and neurodegenerative disease. Iron overload might also increase the risk of chronic disease in HH-free individuals. Nevertheless, whether iron tissue accumulation in those unaffected by genetic disorders is due to high dietary iron intakes is not yet fully understood (1).

Cancer

Hereditary hemochromatosis that is characterized by abnormal hepatic iron accumulation is a risk factor for liver cancer (hepatocellular carcinoma; HCC). Iron accumulation is thought to function as a carcinogen by increasing oxidative stress that causes damage to lipids, proteins, and DNA. A meta-analysis of nine observational studies found an increased HCC risk with the C282Y mutation in the *HFE* gene of healthy participants and patients with chronic liver disease (see Iron Overload) (85). Other meta-analyses have reported associations between *HFE* gene mutations C282Y and H63D and increased risks of overall cancer (86, 87). However, studies reporting on *HFE* gene mutations and risk of cancer at extra-hepatic sites are rather scarce and/or inconsistent. Some, but not all, observational studies found significant associations between the C282Y mutation and risk of colorectal (88), breast (88, 89), and epithelial ovarian cancer (90). The presence of the H63D mutation in the *HFE* gene was linked to an increased risk of leukemia (91, 92) and gastric cancer (93).

Whether high dietary iron could increase the risk of cancer in individuals without hemochromatosis has also been investigated. The consumption of red or processed meat (but not white meat), rich in heme iron, has been linked to an increased risk of colorectal cancer (CRC) (94). Exposure to carcinogenic compounds (called heterocyclic amines) generated when meat is cooked at high temperatures and to carcinogenic N-nitroso compounds formed in the gastrointestinal tract following consumption of red and processed meat may explain such an association (95). Several meta-analyses of observational studies have also suggested a potential association of heme iron in red meat with CRC (96-98). This has been explained by an increased exposure of colonic cells to potentially damaging N-nitroso compounds and lipid peroxidation end-products derived from heme iron-catalyzed reactions (99). Further, recent results from the large European Prospective Investigation into Cancer and Nutrition (EPIC) study suggested a higher risk of esophageal adenocarcinoma with high intakes of red/processed meat and heme iron (100).

Cardiovascular disease

Experimental studies have suggested a role for iron-induced oxidative stress in vessel wall damage and the development of atherosclerosis, which underlies most forms of cardiovascular disease (101). However, epidemiological studies of iron nutritional status and cardiovascular disease in humans have yielded conflicting results. A recent systematic review and meta-analysis of 17 prospective cohort studies in 156,427 participants (9,236 cases of coronary heart disease [CHD] or myocardial infarction [MI]) did not find evidence to support the existence of strong associations between a number of different measures of iron status and CHD/MI (102). Only individuals in the highest versus lowest tertile of serum transferrin saturation exhibited an 18% lower incidence of CHD/MI (102). Another meta-analysis of 21 prospective studies found serum transferrin saturation and serum iron to be inversely associated with the risk of CHD. However, the authors noted that most studies failed to adjust for the confounding effects of inflammation (103). The review also reported an inverse association between CHD incidence and total dietary iron intake, but dietary heme iron was positively associated with CHD incidence (103). Although the relationship between iron stores and CHD/MI requires further clarification, it would be prudent for those who are not at risk of iron deficiency (e.g., adult men and postmenopausal women) to avoid excess iron intake (see the LPI Rx for Health).

Type 2 diabetes mellitus and metabolic syndrome

Individuals with hereditary hemochromatosis (HH) are known to be at a heightened risk of developing type 2 diabetes mellitus (104). Increasing evidence also suggests a role for iron excess in the pathogenesis of type 2 diabetes independent of hemochromatosis. Cross-sectional, case-control, and prospective cohort studies have reported an increased risk of type 2 diabetes (105) and metabolic syndrome (106) with high versus low ferritin concentrations (reflecting iron body stores) after adjustment for inflammation. It is currently unclear how other indices of iron status relate to the risk of type 2 diabetes (107-110). Iron overload-induced oxidative stress in patients with HH is thought to damage pancreatic β-cells and impair insulin secretion. In subjects free of HH, iron excess might damage the liver, interfering with glucose metabolism and triggering insulin resistance, rather than impair β-cell function (111, 112). Iron removal by phlebotomy has been shown to improve metabolic parameters in subjects with type 2 diabetes (113) and metabolic syndrome (114). Additional randomized controlled trials are needed to determine whether lowering body stores of iron will aid in the prevention of type 2 diabetes and metabolic syndrome.

Neurodegenerative disease

Iron is required for normal brain and nerve function through its involvement in cellular metabolism, as well as in the synthesis of neurotransmitters and myelin. Deregulation of iron homeostasis has been observed in a number of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) (115-117). The abnormal accumulation of iron in the brain does not appear to be a result of increased dietary iron, but rather a disruption in the complex process of cellular iron regulation (117). Brain iron accumulation can result in increased oxidative stress, and the brain is particularly susceptible to oxidative damage. Mechanisms behind the disruption of iron homeostasis in the brain of patients affected by neurodegenerative disease are actively being investigated. For example, studies using genetically modified mouse models indicated that the suppression of amyloid precursor protein (APP) expression by upstream nitric oxide (NO) elevation (11) or loss of Tau protein (12) could impair neuronal export of iron and lead to iron accumulation in specific brain regions affected in Parkinson's disease. A pilot, double-blind, placebo-controlled trial in patients with early-stage Parkinson's disease demonstrated oral administration of the iron chelator, deferiprone, for 12 months reduced iron deposition in the part of the brain called substantia nigra and improved motor performance without compromising systemic iron homeostasis (118, 119).

Safety

Toxicity

Overdose

Accidental overdose of iron-containing products is the single largest cause of poisoning fatalities in children under six years of age. Although the oral lethal dose of elemental iron is approximately 180 to 250 mg/kg of body weight, considerably less has been fatal. Symptoms of acute toxicity may occur with iron doses of 20 to 60 mg/kg of body weight. Iron overdose is an emergency situation because the severity of iron toxicity is related to the amount of elemental iron absorbed. Acute iron poisoning produces symptoms in four stages: (1) Within one to six hours of ingestion, symptoms may include nausea, vomiting, abdominal pain, tarry stools, lethargy, weak and rapid pulse, low blood pressure, fever, difficulty breathing, and coma; (2) If not immediately fatal, symptoms may subside for about 24 hours; (3) Symptoms may return 12 to 48 hours after iron ingestion and may include serious signs of failure in the following organ systems: cardiovascular, kidney, liver, hematologic (blood), and central nervous system; and (4) Long-term damage to the central nervous system, liver (cirrhosis), and stomach may develop two to six weeks after ingestion (25, 120).

Adverse effects

At therapeutic levels used to treat iron deficiency, iron supplements may cause gastrointestinal irritation, nausea, vomiting, diarrhea, or constipation. Stools will often appear darker in color. Iron-containing liquids can temporarily stain teeth, but diluting the liquid helps to prevent this effect (120). Taking iron supplements with food instead of on an empty stomach may relieve gastrointestinal effects. The Food and Nutrition Board (FNB) of the Institute of Medicine based the tolerable upper intake level (UL) for iron on the prevention of gastrointestinal distress (**Table 3**). The UL for adolescents (14-18 years) and adults, including pregnant and breast-feeding women, is 45 mg/day. It should be noted that the UL is not meant to apply to individuals being treated with iron under close medical supervision. Individuals with hereditary hemochromatosis or other conditions of iron overload, as well as individuals with alcoholic cirrhosis and other liver diseases, may experience adverse effects at iron intake levels below the UL (25).

Table 3. Tolerable Upper Intake Level (UL) for Iron

Age Group	UL (mg/day)
Infants 0-12 months	40
Children 1-13 years	40
Adolescents 14-18 years	45
Adults 19 years and older	45

Drug interactions

Medications that decrease stomach acidity, such as antacids, histamine (H_2) receptor antagonists (e.g., cimetidine, ranitidine), and proton-pump inhibitors (e.g., omeprazole, lansoprazole), may impair iron absorption. Taking iron supplements at the same time as the following medications may result in decreased absorption and efficacy of the medication: carbidopa and levodopa (Sinemet), levothyroxine (Synthroid, Levoxyl), methyldopa (Aldomet), penicillamine (Cuprimine, Depen), quinolones, tetracyclines, and bisphosphonates (120). Therefore, it is best to take these medications two hours apart from iron supplements. Cholestyramine (Questran) and colestipol (Colestid), used to lower blood cholesterol concentrations, should also be taken at least four hours apart from iron supplements because they may interfere with iron absorption (121).

Does iron supplementation increase the risk of malaria in malaria-endemic regions?

Despite the critical functions of iron in the immune response, the nature of the relationship between iron status and susceptibility to infection, especially with respect to malaria, has been controversial. Because iron withholding is a recognized defense mechanism against pathogens (see Iron withholding defense during infection), concerns have been raised regarding the safety of iron supplementation, especially in iron-replete children living in malaria-endemic regions (122).

Iron supplementation of children residing in the tropics has been associated with increased risk of clinical malaria and other infections like pneumonia (123, 124). A randomized controlled trial in 24,076 children (ages, 1-35 months) living in a malaria-endemic region of eastern Africa (Tanzania) investigated the effects of supplemental iron and folic acid, with or without zinc, compared to the effects of zinc alone or a placebo, on all-cause mortality and hospital admissions (125). The administration of iron, folic acid, and/or zinc was found to increase the risk of serious adverse effects, hospital admission, and death, and was therefore prematurely halted. Further analyses of the trial revealed that iron-replete children were more likely than iron deficient-children (with or without anemia) to be at risk of adverse effects following iron supplementation (125). Such a potential risk of adverse effects with routine iron supplementation was not observed in preschool children in settings without malaria (southern Nepal) (126).

A recent review of 35 trials indicated that iron supplementation did not increase the risk of clinical malaria or other parasitic diseases, infections, and all-cause mortality in children living in malaria-endemic regions in which prevention and management of malaria are available (127). Moreover, a pooled analysis of three high-quality trials demonstrated that supplemental iron combined with anti-malarial treatment protected children against clinical malaria and improved hematological parameters (127). The World Health Organization (WHO) currently recommends the provision of iron supplementation in infants and children, together with measures of malaria prevention, diagnosis, and treatment in malaria-endemic areas (128).

Linus Pauling Institute Recommendation

Following the RDA for iron should provide sufficient iron to prevent deficiency without causing adverse effects in most individuals. Although sufficient iron can be obtained through a varied diet, a considerable number of people do not consume adequate iron to prevent deficiency. A multivitamin/mineral supplement containing 100% of the daily value (DV) for iron provides 18 mg of elemental iron. While this amount of iron may be beneficial for premenopausal women, it is well above the RDA for men and postmenopausal women.

Adult men and postmenopausal women

Since hereditary hemochromatosis is not uncommon and the effects of long-term dietary iron excess on chronic disease risk are not yet clear, men and postmenopausal women who are not at risk of iron deficiency should take a multivitamin/mineral supplement without iron. A number of multivitamins formulated specifically for men or those over 50 years of age do not contain iron.

Older adults (>50 years)

Moderately elevated iron stores might be much more common than iron deficiency in middle-age and older individuals (129). Thus, older adults should not generally take nutritional supplements containing iron unless they have been diagnosed with iron deficiency. Moreover, it is extremely important to determine the underlying cause of the iron deficiency, rather than simply treating it with iron supplements (see The Recommended Dietary Allowance).

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Magnesium

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EspañolF

Summary

- Magnesium is an essential mineral and a cofactor for hundreds of enzymes. Magnesium is involved in many physiologic pathways, including energy production, nucleic acid and protein synthesis, ion transport, cell signaling, and also has structural functions. *(More information)*
- Severe magnesium deficiency can impede vitamin D and calcium homeostasis. Certain individuals are more susceptible to magnesium deficiency, especially those with gastrointestinal or renal disorders, those suffering from chronic alcoholism, and older people. *(More information)*
- Inadequate dietary intakes and/or low serum concentrations of magnesium have been associated with increased risk of cardiovascular disease, osteoporosis, and metabolic disorders, including metabolic syndrome, hypertension, and type 2 diabetes mellitus. Preliminary studies have shown that magnesium improved insulin sensitivity in individuals at risk for type 2 diabetes mellitus. Randomized controlled trials have also investigated the role of magnesium supplementation in the prevention of complications following stroke or heart surgery. *(More information)*
- Magnesium sulfate is used in obstetric care for the prevention of seizures in pregnant women with preeclampsia or eclampsia. Observational studies and randomized controlled trials also support a role for magnesium in preventing brain damage in premature infants. *(More information)*
- The use of magnesium supplementation is currently being explored in the management of various conditions, including hypertension, cardiovascular disease, type 2 diabetes mellitus, asthma and pain. *(More information)*
- About half of the US adult population may have insufficient magnesium intakes to support nutritional adequacy. Dietary sources rich in magnesium include green leafy vegetables, unrefined grains, legumes, beans, and nuts. *(More information)*
- The tolerable upper intake level (UL) for supplemental magnesium is 350 mg/day. Excessive intake of supplemental magnesium can result in adverse effects, especially in individuals with impaired kidney functions. *(More information)*

Magnesium plays important roles in the structure and the function of the human body. The adult human body contains about 25 grams (g) of magnesium. About 50 to 60% of all the magnesium in the body is found in the skeleton and the remainder is found in soft tissue, primarily in muscle. Magnesium is the second most abundant intracellular cation after potassium. Blood contains less than 1% of total body magnesium. Only the free, ionized form of magnesium (Mg^{2+}) is physiologically active. Protein-bound and chelated magnesium serve to buffer the pool of free, ionized magnesium (1).

Function

Magnesium is involved in more than 300 essential metabolic reactions, some of which are discussed below (2).

Energy production

The metabolism of carbohydrates and fats to produce energy requires numerous magnesium-dependent chemical reactions. Magnesium is required by the adenosine triphosphate (ATP)-synthesizing protein in mitochondria. ATP, the molecule that provides energy for almost all metabolic processes, exists primarily as a complex with magnesium (MgATP) (3).

Synthesis of essential molecules

Magnesium is required for a number of steps during synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins. Several enzymes participating in the synthesis of carbohydrates and lipids require magnesium for their activity. Glutathione, an important antioxidant, requires magnesium for its synthesis (3).

Structural roles

Magnesium plays a structural role in bone, cell membranes, and chromosomes (3).

Ion transport across cell membranes

Magnesium is required for the active transport of ions like potassium and calcium across cell membranes. Through its role in ion transport systems, magnesium affects the conduction of nerve impulses, muscle contraction, and normal heart rhythm (3).

Cell signaling

Cell signaling requires MgATP for the phosphorylation of proteins and the formation of the cell-signaling molecule, cyclic adenosine monophosphate (cAMP). cAMP is involved in many processes, including the secretion of parathyroid hormone (PTH) from the parathyroid glands (see the articles on Vitamin D and Calcium for information on the role of PTH in the body) (3).

Cell migration

Calcium and magnesium concentrations in the fluid surrounding cells affect the migration of a number of different cell types. Such effects on cell migration may be important in wound healing (3).

Nutrient interactions

Zinc

High doses of zinc in supplemental form apparently interfere with the absorption of magnesium. One study reported that zinc supplements of 142 mg/day (well above the tolerable upper intake level (UL) of 40 mg/day for zinc) in healthy adult males significantly decreased magnesium absorption and disrupted magnesium balance (the difference between magnesium intake and magnesium loss) (4).

Fiber

Large increases in the intake of dietary fiber have been found to decrease magnesium utilization in experimental studies. However, the extent to which dietary fiber affects magnesium nutritional status in individuals with a varied diet outside the laboratory is not clear (2, 3).

Protein

Dietary protein intake may affect magnesium absorption. One study in adolescent boys found that magnesium absorption was directly related to protein intake, with magnesium absorption the lowest when protein intake was less than 30 g/day (5).

Vitamin D and calcium

The active form of vitamin D (calcitriol) may slightly increase intestinal absorption of magnesium (6). However, it is not clear whether magnesium absorption is calcitriol-dependent as is the absorption of calcium and phosphate. High calcium intake has not been found to affect magnesium balance in most studies. Inadequate blood magnesium concentrations are known to result in low blood calcium concentrations, resistance to parathyroid hormone (PTH) action, and resistance to some of the effects of vitamin D (2, 3).

Deficiency

Risk factors

Magnesium deficiency in healthy individuals who are consuming a balanced diet is quite rare because magnesium is abundant in both plant and animal foods and because the kidneys are able to limit urinary excretion of magnesium when intake is low. The following conditions increase the risk of magnesium deficiency (7):

- Gastrointestinal disorders: Prolonged diarrhea, Crohn's disease, malabsorption syndromes, celiac disease, surgical removal of a portion of the small intestine, and intestinal inflammation due to radiation may all lead to magnesium depletion.
- Renal disorders (magnesium wasting): Diabetes mellitus and long-term use of certain diuretics (see Drug interactions) may result in increased urinary loss of magnesium. Multiple other medications can also result in renal magnesium wasting (3).
- Endocrine and metabolic disorders: Several conditions, such as diabetes mellitus, parathyroid gland disorders, phosphate depletion, primary aldosteronism, and even excessive lactation, can lead to magnesium depletion.

Poor dietary intake, gastrointestinal problems, and increased urinary loss of magnesium may all contribute to magnesium depletion in people suffering from alcoholism. Older adults have relatively low dietary intakes of magnesium (8, 9). Intestinal magnesium absorption tends to decrease with age, and urinary magnesium excretion tends to increase with age; thus, suboptimal dietary magnesium intake may increase the risk of magnesium depletion in the elderly (2).

Signs and symptoms

Although severe magnesium deficiency is uncommon, it has been induced experimentally. When magnesium deficiency was induced in humans, the earliest sign was a decrease in serum magnesium concentration. Hypomagnesemia usually describes serum magnesium concentrations less than 0.74 millimoles/liter (mmol/L) or 1.40 milliequivalents/liter (mEq/L) or 1.70 milligrams/deciliter (mg/dL). Over time, serum calcium concentration also began to decrease (hypocalcemia) despite adequate dietary calcium. Hypocalcemia persisted despite increased secretion of parathyroid hormone (PTH), which regulates calcium homeostasis. Usually, increased PTH secretion quickly results in the mobilization of calcium from bone and normalization of blood calcium concentration. As the magnesium depletion progressed, PTH secretion diminished to low concentrations. In addition to hypomagnesemia, signs of severe magnesium deficiency included hypocalcemia, low serum potassium concentrations (hypokalemia), retention of sodium, low circulating PTH concentrations, neurological and muscular symptoms (tremor, muscle spasms, tetany), loss of appetite, nausea, vomiting, and personality changes (3).

While mild magnesium deficiency may not elicit clinical symptoms, it may be associated with an increased risk of developing chronic diseases (see Disease Prevention) (1).

Assessing magnesium status

There is currently no reliable indicator of magnesium status. The magnesium tolerance test, which basically determines magnesium retention (using 24-h urine collection) following the intravenous administration of magnesium, is considered to be the gold standard (1). If this method is a good indicator of hypomagnesemia in adults, it appears to be poorly sensitive to changes in magnesium status in healthy people. Moreover, the method is invasive and cumbersome, and thus difficult to use routinely (10). Another method to assess magnesium status is through measurements of plasma ionized magnesium, which represents the physiologically active form of magnesium. However, it is unknown whether plasma ionized magnesium reflect body stores (10).

In practice, magnesium status is usually determined through assessments of dietary magnesium intake, serum magnesium concentration, and/or urinary magnesium concentration (10). However, each of these indicators has limitations. Although predominantly used in epidemiological studies and the sole indicator available to clinicians, serum magnesium concentration has been found to poorly respond to magnesium supplementation. Regarding dietary intakes of magnesium, about 30 to 40% of ingested magnesium is absorbed, yet absorption varies with the amount of magnesium ingested and with the food matrix composition. Finally, a state of magnesium deficiency has not been associated to a clear cutoff concentration of magnesium in the urine. Urinary magnesium concentration fluctuates rapidly with dietary intakes, but measurements of 24-hour urinary magnesium can be used in addition to other indicators to assess population status. Presently, a combination of all three markers — dietary, serum, and urinary magnesium — may be used to get a valid assessment of magnesium status (reviewed in 10).

The Recommended Dietary Allowance (RDA)

In 1997, the Food and Nutrition Board of the Institute of Medicine increased the Recommended Dietary Allowance (RDA) for magnesium, based on the results of tightly controlled balance studies that utilized more accurate methods of measuring magnesium (**Table 1**) (2). Balance studies are useful for determining the amount of a nutrient that will prevent deficiency; however, such studies provide little information regarding the amount of a nutrient required for chronic disease prevention or optimal health.

Table 1. Recommended Dietary Allowance (RDA) for Magnesium

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	30 (AI*)	30 (AI)
Infants	7-12 months	75 (AI)	75 (AI)
Children	1-3 years	80	80
Children	4-8 years	130	130
Children	9-13 years	240	240
Adolescents	14-18 years	410	360
Adults	19-30 years	400	310
Adults	31 years and older	420	320
Pregnancy	18 years and younger	-	400
Pregnancy	19-30 years	-	350
Pregnancy	31 years and older	-	360
Breast-feeding	18 years and younger	-	360
Breast-feeding	19-30 years	-	310
Breast-feeding	31 years and older	-	320
*Adequate Intake			

Disease Prevention

Metabolic syndrome

Metabolic syndrome refers to the concomitant presentation of several metabolic disorders in an individual, including dyslipidemia, hypertension, insulin resistance, and obesity (11). People with metabolic syndrome are at greater risk of developing type 2 diabetes mellitus, cardiovascular disease, and some types of cancer (12-14). A 2015 analysis of data from the US National Health and Nutrition Examination Survey (NHANES 2001-2010) in 9,148 adults (mean age, 50 years) found a 32% lower risk of metabolic syndrome in those in the highest versus lowest quantile of magnesium intake (≥355 mg/day versus <197 mg/day) (15). Several meta-analyses of primarily cross-sectional studies have also reported an inverse association between dietary magnesium intake and risk of metabolic syndrome (16-18). Moreover, lower serum magnesium concentrations have been reported in individuals with metabolic syndrome compared to controls (18, 19). However, circulating magnesium represents only 1% of total body stores and is tightly regulated; thus, serum magnesium concentrations do not best reflect magnesium status (1). At present, additional evidence is needed from prospectively designed studies to inform the potential relationship between dietary and circulating magnesium and the risk of metabolic syndrome.

Systemic inflammation, which contributes to the development of metabolic disorders, has been inversely correlated with magnesium intakes in a cross-sectional study of 11,686 women (≥45 years). In this study, the lowest prevalence of metabolic syndrome was found in the group of women in the highest quintile of magnesium intakes (median intake, 422 mg/day) (20). Several randomized controlled trials also reported a reduction in circulating C-reactive protein (CRP) — a marker of inflammation — following oral magnesium supplementation (21). This might constitute a potential mechanism through which magnesium could play a role in the prevention of metabolic disorders.

Cardiovascular disease

Hypertension (high blood pressure)

Large prospective cohort studies have examined the relationship between magnesium and blood pressure. However, the fact that foods high in magnesium (fruit, vegetables, whole grains) are frequently high in potassium and dietary fiber has made it difficult to evaluate the independent effect of magnesium on blood pressure. Findings from large cohorts, including the Health Professionals Follow-up Study (HPFS) (22), the Nurses' Health Study (NHS) (23), the Atherosclerosis Risk in Communities (ARIC) study (24), and the Coronary Artery Risk Development in Young Adults (CARDIA) study (25), have been summarized in a recent meta-analysis (26). The pooled analysis of seven prospective studies showed an 8% lower risk of hypertension with higher versus lower dietary magnesium intakes (26). In one of these studies, data from 5,511 men and women followed for a median period of 7.6 years found that the highest concentrations of urinary magnesium corresponded to a 25% reduction in the risk of hypertension, whereas there was no association between plasma magnesium concentrations and the risk of hypertension (27). There was also no evidence of an association between circulating magnesium concentrations and the risk of hypertension in a meta-analysis of three prospective cohort studies (26).

The relationship between magnesium intake and risk of hypertension suggests that improving diet quality or using magnesium supplements might play a role in the prevention of hypertension in those with inadequate dietary intakes.

Vascular calcification

The buildup of plaque inside arterial walls — a process called atherosclerosis — is an early event in the development of cardiovascular disease. The calcification of atherosclerotic plaques that occurs with the progression of atherosclerosis has been associated with a three- to four-fold increase in the risk of cardiovascular events and mortality (28).

Individuals with chronic kidney disease (CKD): Abnormalities in mineral and bone metabolism are not uncommon in individuals with impaired kidney function and have been associated with an increased risk of cardiovascular disease and mortality (29, 30). In particular, elevated blood phosphorus concentration and increased deposition of calcium phosphate within the vasculature are thought to promote vascular calcification. Since magnesium can function as a calcium antagonist, it has been suggested that it could be utilized to slow down or reverse the calcification of vessels observed in patients with CKD. In a cross-sectional study in patients with pre-dialysis CKD, higher serum magnesium concentrations were associated with lower coronary artery calcification density scores in those in the higher end of normal serum phosphorus concentrations (i.e., ≥3.4 mg/dL) (31). One small randomized, placebo-controlled trial in participants with pre-dialysis CKD examined the effect of oral, slow-release magnesium hydroxide on the calcification propensity of serum by measuring the time needed for primary calciprotein particles (containing amorphous calcium phosphate) to transform into secondary calciprotein particles (containing crystalline hydroxyapatite) (32). Increased serum calcification propensity has been associated with greater risk of mortality in patients with impaired kidney function (33, 34). The trial found an increase in serum magnesium concentration and a reduction in serum calcification propensity — i.e., an increase in the time needed for 50% of the transformation to occur (T_{50}) — with 720 mg/day of supplemental magnesium for eight weeks compared to placebo (32). Serum calcification propensity was also reduced when magnesium concentration was increased (from 1 to 2 mEq/L for 28 days) in the dialysate of patients with established kidney failure (35). A larger randomized controlled trial in patients with pre-dialysis CKD is underway to examine further the effect of oral magnesium on markers of vascular calcification, markers of mineral and bone metabolism, incidence of cardiovascular events, and deterioration of kidney function (36).

Individuals with normal kidney function: The cross-sectional analysis of data from 2,695 middle-aged participants in the Framingham Heart Study showed that the odds of having coronary artery calcification was 58% lower in those in the highest versus lowest quartile of total magnesium intakes (median values, 427 mg/day versus 259 mg/day) (37). Serum magnesium concentration was also found to be inversely associated with vascular calcification in recent population-based cross-sectional studies (38-40). No research has yet examined whether improving magnesium status of generally healthy people could play a role in atherosclerosis prevention.

magnesium status of generally healthy people could play a role in atherosclerosis prevention.

Risk of cardiovascular disease

Dietary magnesium intakes: Several large prospective cohort studies, including the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), have examined magnesium intakes in relation to cardiovascular outcomes. In the most recent analysis of the NHS, which followed nearly 90,000 female nurses for 28 years, those in the highest quintile of magnesium intake had a 39% lower risk of fatal myocardial infarction (but not nonfatal coronary heart disease [CHD]) compared to those in the lowest quintile (>342 mg/day versus <246 mg/day) (41). A meta-analysis of nine prospective cohort studies, mostly conducted in participants without cardiovascular disease at baseline, reported a 22% lower risk of CHD per 200 mg/day incremental intake in dietary magnesium (42). A more recent meta-analysis by Fang et al. (43) included six studies and reported a 10% lower risk of CHD with higher versus lower dietary magnesium intakes.

Higher magnesium intakes were associated with an 8 to 11% reduction in stroke risk in two meta-analyses of prospective studies, each including over 240,000 participants (44, 45). The most recent pooled analysis of 14 studies found a 12% lower risk of stroke with higher versus lower magnesium intakes and estimated a 7% risk reduction of stroke associated with each 100-mg increment in daily magnesium intake (43).

Only two prospective studies have examined the risk of heart failure in relation to magnesium intakes. The pooled analysis suggested a 31% lower risk of heart failure with higher dietary magnesium intakes (43).

Finally, a meta-analysis of 13 prospective studies in over 475,000 participants reported that the risk of total cardiovascular events, including stroke, nonfatal myocardial infarction, and CHD, was 15% lower in individuals with higher intakes of magnesium (46). However, in the recent meta-analysis of eight studies by Fang et al. (43), there was no association between dietary magnesium intake and risk of total cardiovascular disease.

It is important to note that while these prospective cohort studies assessed the association between dietary magnesium and cardiovascular disease, they did not account for the use of supplemental magnesium by a significant fraction of participants.

Serum magnesium concentrations: One large prospective study (almost 14,000 men and women) associated higher serum magnesium concentrations with a lower risk of CHD in women but not in men (47). This study was included in a meta-analysis of four studies that showed no evidence of a reduced risk of CHD with increasing serum magnesium concentrations (42). In contrast, a 0.2 mmol/L increment in serum magnesium concentration was associated with a 30% lower risk of total cardiovascular disease in a pooled analysis of eight prospective cohort studies (42). In the recently published British Regional Heart Study that followed 3,523 men for a mean 15 years, there was no association between serum magnesium concentration and incidental CHD events, yet serum magnesium concentration was inversely associated with the risk of heart failure (48).

Cardiovascular mortality

A number of early studies found lower cardiovascular-related mortality in populations who routinely consume "hard" water. Hard (alkaline) water is generally high in magnesium but may also contain more calcium and fluoride than "soft" water, making the cardioprotective effects of hard water difficult to attribute to magnesium alone (49). Additionally, meta-analyses of prospective studies have found no associations between magnesium intake and cardiovascular (50) or all-cause mortality (43). In a prospective analysis of NHANES data from 14,353 participants, followed for a median period of 28.6 years, the risk of all-cause and stroke mortality was significantly increased in those with low rather than normal serum concentrations of magnesium (<0.7 mmol/L versus 0.8-0.89 mmol/L) (51). In contrast, hypermagnesemia (serum magnesium concentration >0.89 mmol/L) — rather than hypomagnesemia — in people with heart failure was associated with an increased risk of cardiovascular and all-cause mortality (52).

Aneurysmal subarachnoid hemorrhage

Occurrence of hypomagnesemia has been reported in patients who suffered from a subarachnoid hemorrhage (a type of stroke) caused by the rupture of a cerebral aneurysm (53). Poor neurologic outcomes following an aneurysmal subarachnoid hemorrhage (aSAH) have been linked to inappropriate calcium-dependent contraction of arteries (known as cerebral arterial vasospasm), leading to delayed cerebral ischemia (54). Because magnesium is a calcium antagonist and potent vasodilator, several randomized controlled trials have examined whether intravenous magnesium sulfate infusions could reduce the incidence of vasospasm after aSAH. A meta-analysis of nine randomized controlled trials found that magnesium therapy after aSAH significantly reduced vasospasm but failed to prevent neurologic deterioration or decrease the risk of death (55). Another meta-analysis of 13 trials in 2,413 aSAH sufferers concluded that the infusion of magnesium sulfate had no benefit regarding neurologic outcome and mortality, despite a reduction in the incidence of delayed cerebral ischemia (56). The post-hoc analysis of a small randomized controlled trial suggested that maintaining magnesium sulfate infusion for 10 days post-aSAH or until signs of vasospasm disappear might protect against secondary cerebral infarction when markers of vasoconstriction and reduced brain perfusion are present (57, 58). Current evidence does not support the use of magnesium supplementation in clinical practice for aSAH patients beyond magnesium status normalization.

Complications of heart surgery

Atrial arrhythmia (also called atrial fibrillation) is a condition defined as the occurrence of persistent heart rate abnormalities; such arrhythmias often complicate the recovery of patients after cardiac surgery. The use of magnesium in the prophylaxis of postoperative atrial arrhythmia after coronary artery bypass grafting has been evaluated as a sole or adjunctive agent to classical antiarrhythmic molecules (namely, β-blockers and amiodarone) in several prospective, randomized controlled trials. A meta-analysis of 21 intervention studies showed that intravenous magnesium infusions could significantly reduce postoperative atrial arrhythmia in treated compared to untreated patients (59). The results of a more recent meta-analysis of 22 placebo-controlled trials suggested that magnesium may effectively reduce atrial arrhythmia when administered post-operatively, as a bolus, and for more than 24 hours (60). However, another meta-analysis of four trials found that magnesium was no more effective than other antiarrhythmic agents (60). Moreover, the meta-analysis of five randomized controlled trials also suggested that intravenous magnesium added to β-blocker treatment did not decrease the risk of atrial arrhythmia compared to β-blocker alone and was associated with more adverse effects (bradycardia and hypotension) (61). Presently, high-quality evidence is still lacking to support the use of magnesium in the prophylaxis of post-operative atrial fibrillation and other arrhythmias in patients with contraindications to first-line antiarrhythmic agents (60).

Diabetes mellitus

Public health concerns regarding the epidemics of obesity and type 2 diabetes mellitus and the prominent role of magnesium in glucose metabolism have led scientists to investigate the relationship between magnesium intake and type 2 diabetes mellitus. A prospective cohort study that followed more than 25,000 individuals, 35 to 65 years of age, for seven years found no difference in incidence of type 2 diabetes mellitus when comparing the highest (377 mg/day) quintile of magnesium intake to the lowest quintile (268 mg/day) (62). However, inclusion of this study in a meta-analysis of eight cohort studies showed that the risk of type 2 diabetes was inversely correlated with magnesium intake (62). The most recent meta-analysis of 25 prospective cohort studies, including 637,922 individuals and 26,828 new cases of type 2 diabetes mellitus, found that higher magnesium intakes were associated with a 17% lower risk of type 2 diabetes mellitus (63). Several meta-analyses conducted to date reported an 8 to 15% decrease in the risk of developing type 2 diabetes mellitus with each 100 mg-increment in dietary magnesium intake (63-66).

Insulin resistance, characterized by alterations in both insulin secretion by the pancreas and insulin action on target tissues, has been linked to inadequate magnesium status. A cross-sectional analysis of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, which included 15 cohorts with a total of 52,684 diabetes-free participants, showed that magnesium intakes were inversely associated with fasting insulin concentrations after multiple adjustments, including various lifestyle factors, body mass index (BMI), caffeine intake, and fiber intake (65). It is thought that pancreatic β-cells, which secrete insulin, could become less responsive to changes in insulin sensitivity in magnesium-deficient subjects (67). A randomized, double-blind, placebo-controlled trial that enrolled 97 healthy adults with significant hypomagnesemia (serum magnesium concentration ≤0.70 mmol/L) showed that daily consumption of 638 mg of magnesium (from a solution of magnesium chloride) for three months improved the function of pancreatic β-cells, resulting in lower fasting glucose and insulin concentrations (68). In a follow-up randomized controlled trial, the administration of 382 mg/day of magnesium for four months to participants (mean age, 42 years) with both hypomagnesemia (serum magnesium concentration <0.74 mmoles/L) and impaired fasting glucose improved serum magnesium concentrations, as well as fasting and post-load glucose concentrations (69). Other metabolic markers, including serum triglycerides, HDL-cholesterol, and a measure of insulin resistance, also improved in magnesium- versus placebo-treated individuals (69). Additionally, similar metabolic improvements have been reported following the supplementation of magnesium (382 mg/day for four months) to participants who were both hypomagnesemic and lean yet metabolically obese (i.e., with metabolic disorders usually associated with obesity) (70). In another study, supplementation with 365 mg/day of magnesium (from magnesium aspartate hydrochloride) for six months reduced insulin resistance in 27 overweight individuals with normal values of serum and intracellular magnesium (71). This latter study suggests that magnesium might have additional effects on glucose tolerance and insulin sensitivity that go beyond the normalization of serum magnesium concentrations in hypomagnesemic individuals.

Osteoporosis

Although decreased bone mineral density (BMD) is the primary feature of osteoporosis, other osteoporotic changes in the collagenous matrix and mineral composition of bone may result in bones that are brittle and more susceptible to fracture (72). Around 60% of total body magnesium is stored in the skeleton and is known to influence both bone matrix and bone mineral metabolism. Magnesium at the surface of bones is also available for dynamic exchange with blood (73). As the magnesium content of bone mineral decreases, hydroxyapatite crystals of bone may become larger and more brittle. Some studies have found lower magnesium content and larger hydroxyapatite crystals in bones of women with osteoporosis compared to disease-free women (74). Inadequate serum magnesium concentrations are known to result in low serum calcium concentrations, resistance to parathyroid hormone (PTH) action, and resistance to some of the effects of vitamin D (calcitriol), all of which can lead to increased bone loss (see the articles on Vitamin D and Calcium). Lower serum magnesium concentrations may not be unusual in postmenopausal women with osteoporosis (75), and hypomagnesemia has been reported as an adverse effect of using the prescription drug teriparatide (Forteo) in the treatment of osteoporosis (76).

Higher dietary magnesium intakes have been associated with increased site-specific (77) and total-body BMD (78) in observational studies, including studies of older adults. More recently, a large cohort study conducted in almost two-thirds of the Norwegian population found the level of magnesium in drinking water to be inversely associated with the risk of hip fracture (79). In the Women's Health Initiative study, data analysis from 4,778 participants (mean age, 63 years) followed for about seven years showed that higher magnesium intakes were associated with higher hip and whole-body BMD but not with reduced hip or total fractures (80). Moreover, the highest versus lowest quintile of total magnesium intakes was associated with a 23% increased risk of lower arm and wrist fractures (80). In a case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, which included 5,319 individuals, total magnesium and potassium intakes were found to be inversely associated with heel bone (calcaneus) broadband ultrasound attenuation (BUA) measurements — which are predictive of the risk of incidental fracture — and with the risk of hip fractures (81).

Few studies have addressed the effect of magnesium supplementation on BMD or osteoporosis in humans. In a small group of postmenopausal women with osteoporosis, magnesium supplementation of 750 mg/day for six months followed by 250 mg/day for 18 more months resulted in increased BMD at the wrist after one year, with no further increase after two years of supplementation (82). A study in postmenopausal women who were taking estrogen replacement therapy and a multivitamin supplement found that supplementation with an additional 400 mg/day of magnesium and 600 mg/day of calcium resulted in increased BMD at the heel compared to postmenopausal women receiving estrogen replacement therapy only (83). A more recent randomized controlled study conducted in 20 postmenopausal women with osteoporosis suggested that high-dose supplementation with magnesium citrate (1,830 mg/day) for one month could reduce the rapid rate of bone loss that characterizes osteoporosis (84). Evidence is not yet sufficient to suggest that supplemental magnesium in excess of the RDA could be effective in the prevention of osteoporosis unless normalization of serum magnesium concentration is required (85).

Sarcopenia

Sarcopenia is a condition characterized by a loss of skeletal muscle mass that increases frailty and risk of falls in older adults (86). Several cross-sectional studies have reported a positive association between dietary magnesium intakes and proxy measures of skeletal muscle mass in middle-age and older adults (87-90). A 2014 randomized controlled study in 139 physically active and healthy older women (mean age, 71.5 years) found little-to-no impact of magnesium supplementation (900 mg/day of magnesium oxide) for 12 weeks on body composition and muscle strength, yet the Short Physical Performance Battery [SPPB] test score — a composite indicator of physical function — improved (91). More research is needed to examine further the effect of magnesium supplementation on body composition, muscle strength, and physical performance in older adults, whether physically active or sedentary, and with normal or inadequate magnesium status.

Disease Treatment

The use of pharmacologic doses of magnesium to treat specific disorders is discussed below. Although many of the cited studies utilized supplemental magnesium at doses considerably higher than the tolerable upper intake level (UL), which is 350 mg/day set by the Food and Nutrition Board (see Safety), it is important to note that these studies were all conducted under medical supervision. Because of the potential side effects of high doses of magnesium, especially in the presence of impaired kidney function, any disease treatment trial using oral magnesium doses higher than the UL should be conducted under medical supervision. Moreover, intravenous magnesium has been used in the management of several conditions.

Pregnancy complications

Preeclampsia and eclampsia

Preeclampsia and eclampsia are hypertensive disorders of pregnancy that may occur at any time after 20 weeks' gestation and persist up to six weeks following birth. Preeclampsia (sometimes called toxemia of pregnancy) affects approximately 4% of pregnant women in the US (92). Preeclampsia is defined as the presence of elevated blood pressure (hypertension), protein in the urine, and severe swelling (edema) during pregnancy (93). Eclampsia occurs with the addition of seizures to the triad of preeclamptic symptoms and is a significant cause of perinatal and maternal mortality (93, 94). Although cases of preeclampsia are at high risk of developing eclampsia, one-quarter of eclamptic women do not initially exhibit preeclamptic symptoms (95).

Although lower magnesium concentrations have been reported in the blood and brain of women with preeclampsia than in healthy pregnant women, there is no evidence that magnesium imbalance may cause adverse pregnancy events. A 2014 meta-analysis of 10 randomized controlled trials found no effect of oral magnesium salt administration during normal and at-risk pregnancies on the risk of preeclampsia, perinatal mortality, and small-for-gestational age infants (96).

For many years, high-dose intravenous magnesium sulfate has been the treatment of choice for preventing eclamptic seizures that may occur in association with severe preeclampsia in pregnancy or during labor (97, 98). A systematic review of seven randomized trials in 1,396 women with eclampsia compared the effect of magnesium sulfate administration with diazepam (a known anticonvulsant) treatment on perinatal outcomes. Risks of recurrent seizures and maternal death were significantly reduced by the magnesium regimen compared to diazepam. Moreover, the use of magnesium for the care of eclamptic women resulted in newborns with higher Apgar scores; there was no significant difference in the risk of preterm birth and perinatal mortality (95). Additional research has confirmed that infusion of magnesium sulfate should always be considered in the management of severe preeclampsia and eclampsia to prevent initial and recurrent seizures (99). Moreover, the World Health Organization (WHO) recommends the use of magnesium sulfate — administered either intramuscularly or intravenously — as first-line treatment for the prevention of eclampsia in women with severe preeclampsia, in preference to other anticonvulsants (100). Further research is needed to evaluate the efficacy of magnesium salt infusion in eclampsia prophylaxis in women with mild preeclampsia (101). In addition, it is unclear whether prolonging magnesium use post-partum in women who presented with severe preeclampsia during pregnancy is necessary to lower the risk of eclampsia after delivery (102).

Perinatal neuroprotection

While intravenous magnesium sulfate is included in the medical care of preeclampsia and eclampsia, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine support its use in two additional situations: specific conditions of short-term prolongation of pregnancy and neuroprotection of the fetus in anticipated premature delivery (103).

Preterm birth, which is defined by the premature delivery of an infant between the 20th and 37th weeks of estimated gestation, is associated with an increased risk of perinatal mortality and both short- and long-term morbidity. The ACOG approves the use of different classes of drugs — known as tocolytics — that are meant to delay delivery for long enough so that antenatal corticoids can be used to accelerate lung maturation in the fetus of women at imminent risk of preterm labor (104). A 2014 meta-analysis of 37 trials found that intravenous infusion of magnesium sulfate was no more efficacious than commonly used tocolytics (e.g., β-adrenergic receptor agonists, calcium channel blockers, prostaglandin inhibitors) in delaying delivery or preventing serious infant outcomes (105). Very limited evidence also suggested that high- versus low-dose magnesium infusion may reduce the length of hospital stays in neonates admitted to intensive care units (106).

The relationship between magnesium sulfate and risk of cerebral damage in premature infants has been assessed in observational studies. A meta-analysis of six case-control and five prospective cohort studies showed that the use of magnesium significantly reduced the risk of cerebral palsy, as well as mortality (107). However, the high degree of heterogeneity among the cohort studies and the fact that corticosteroid exposure (which is known to decrease antenatal mortality) was higher in the cases of children exposed to magnesium compared to controls imply a cautious interpretation of the results. Nonetheless, a meta-analysis of five randomized controlled trials, which included 5,493 women at risk of preterm birth and 6,135 babies, found that magnesium therapy given to mothers delivering before term decreased the risk of cerebral palsy by 32% without causing severe adverse maternal events, but this treatment did not reduce the risk of other neurologic impairments or mortality in early childhood (108). Another meta-analysis conducted on five randomized controlled trials found that intravenous magnesium administration to newborns who suffered from perinatal asphyxia could be beneficial in terms of short-term neurologic outcomes, although there was no effect on mortality (109). Additional trials are needed to evaluate the long-term benefits of magnesium in pediatric care.

Cardiovascular disease

Hypertension

While results from intervention studies have not been entirely consistent (2), the latest review of the data highlighted a therapeutic benefit of magnesium supplements in treating hypertension. A 2012 meta-analysis examined 22 randomized, placebo-controlled trials of magnesium supplementation conducted in 1,173 individuals with either normal blood pressure (normotensive) or hypertension (treated with medication or untreated). Oral supplementation with magnesium (mean dose of 410 mg/day; range of 120 to 973 mg/day) for a median period of 11.3 months significantly reduced systolic blood pressure by 2 to 3 mm Hg and diastolic blood pressure by 3 to 4 mm Hg (110); a greater effect was seen at higher doses (≥370 mg/day). The results of 19 of the 22 trials included in the meta-analysis were previously reviewed together with another 25 intervention studies (111). The systematic examination of these 44 trials suggested a blood pressure-lowering effect associated with supplemental magnesium in hypertensive but not in normotensive individuals.

Magnesium doses required to achieve a decrease in blood pressure appeared to depend on whether participants with high blood pressure were treated with antihypertensive medications, including diuretics. Intervention trials on treated participants showed a reduction in hypertension with magnesium doses from 243 mg/day to 486 mg/day, whereas untreated patients required doses above 486 mg/day to achieve a significant decrease in blood pressure. A more recent meta-analysis of randomized controlled studies with 2,028 participants found that supplemental magnesium at a median dose of 368 mg/day (range: 238-960 mg/day) for a median duration of three months (range: 3 weeks-6 months) increased serum magnesium concentration by 0.05 mmol/L (27 trials) and reduced systolic blood pressure by 2 mm Hg and diastolic blood pressure by 1.78 mm Hg (37 trials) (112). A 2017 meta-analysis restricted to trials in participants with underlying preclinical (insulin resistance or prediabetes) or clinical conditions (type 2 diabetes mellitus or coronary heart disease) found a 4.18 mm Hg reduction in systolic blood pressure and a 2.27 mm Hg reduction in diastolic blood pressure with supplemental doses of magnesium ranging between 365 mg/day and 450 mg/day for one to six months (113).

While oral magnesium supplementation may be helpful in hypertensive individuals who are depleted of magnesium due to chronic diuretic use and/or inadequate dietary intake (7), several dietary factors play a role in hypertension. For example, adherence to the DASH diet — a diet rich in fruit, vegetables, and low-fat dairy and low in saturated and total fats — has been linked to significant reductions in systolic and diastolic blood pressures (114). See the topic page: High Blood Pressure.

Atherosclerosis

Vascular endothelial cells line arterial walls where they are in contact with the blood that flows through the circulatory system. Normally functioning vascular endothelium promotes vasodilation when needed, for example, during exercise, and inhibits the formation of blood clots. Conversely, endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities. In cardiovascular disease, chronic inflammation is associated with the formation of atherosclerotic plaques in arteries. Atherosclerosis impairs normal endothelial function, increasing the risk of vasoconstriction and clot formation, which may lead to heart attack or stroke (reviewed in 115). A recent systematic review identified six randomized controlled trials that examined the effect of pharmacologic doses of oral magnesium on vascular endothelial function (116). Three out of six trials, which included individuals with coronary artery disease (117), diabetes mellitus (118), or hypertension (119), reported an improvement in flow-mediated dilation (FMD) with supplemental magnesium compared to control. In other words, the normal dilation response of the brachial (arm) artery to increased blood flow was improved. In contrast, there was no evidence of an effect of magnesium supplementation on FMD in three trials conducted in hemodialysis patients (120) or healthy participants with normal (121) or high body mass index (BMI) (122). A pooled analysis of the six trials in 262 participants found that supplementation with 107 to 730 mg/day of magnesium for one to six months resulted in an overall improvement of FMD, regardless of the health status or baseline magnesium concentrations of participants (116).

The measurement of the thickness of the inner layers of the carotid arteries is sometimes used as a surrogate marker of atherosclerosis (123). Higher serum magnesium concentrations have been associated with reduced carotid intima-media thickness (CIMT) in all women and in Caucasian men participating in the Atherosclerosis Risk in Communities (ARIC) study (124). A meta-analysis of four small (145 participants in total) and heterogeneous intervention studies found no effect of magnesium supplementation (98.6 to 368 mg/day for 2 to 6 months) on CIMT (116).

Survival after myocardial infarction

Results from several randomized, placebo-controlled trials have suggested that an intravenous magnesium administered early after a suspected myocardial infarction could decrease the risk of death. The most influential study was a randomized, placebo-controlled trial in 2,316 patients that found a significant reduction in mortality in the group of patients given intravenous magnesium sulfate within 24 hours of suspected myocardial infarction (7.8% all-cause mortality in the experimental group vs. 10.3% all-cause mortality in the placebo group) (125). Follow-up from one to five years after treatment revealed that the mortality from cardiovascular disease was 21% lower in the magnesium-treated group (126). However, a larger placebo-controlled trial in more than 58,000 patients found no significant reduction in five-week mortality in patients treated with intravenous magnesium sulfate within 24 hours of suspected myocardial infarction, resulting in controversy regarding the efficacy of this treatment (127). A US survey of the treatment of more than 173,000 individuals with acute myocardial infarction found that only 5% were given intravenous magnesium in the first 24 hours post-infarction and that mortality was higher in this group compared to the group of patients not treated with magnesium (128). A 2007 systematic review of 26 clinical trials, including 73,363 participants, concluded that intravenous magnesium administration does not appear to reduce post-myocardial infarction mortality and thus should not be utilized as a treatment (129). Thus, the use of intravenous magnesium sulfate in the therapy of acute myocardial infarction remains controversial.

Diabetes mellitus

Magnesium depletion has been associated with type 1 (insulin-dependent) and type 2 diabetes mellitus, as well as with gestational diabetes. Low serum concentrations of magnesium (hypomagnesemia) have been reported in 13.5 to 47.7% of individuals with type 2 diabetes mellitus (130). One cause of the depletion may be an increased urinary loss of magnesium caused by an increased urinary excretion of glucose that accompanies poorly controlled diabetes. Magnesium depletion has been shown to increase insulin resistance in a few studies and may adversely affect blood glucose control in diabetes mellitus (see also Diabetes mellitus under Disease Prevention) (131). A small study in nine individuals with type 2 diabetes mellitus reported that supplemental magnesium (300 mg/day for 30 days), in the form of a liquid, magnesium-containing salt solution, improved fasting insulin but not fasting glucose concentrations (132). One randomized, double-blind, placebo-controlled study in 63 individuals with type 2 diabetes mellitus and hypomagnesemia found that those taking an oral magnesium chloride solution (638 mg/day of elemental magnesium) for 16 weeks had improved measures of insulin sensitivity and glycemic control compared to those taking a placebo (133). The most recent meta-analysis of nine randomized, double-blind, controlled trials concluded that oral supplemental magnesium lowered fasting plasma glucose concentrations in individuals with diabetes (134). However, magnesium supplementation did not improve other markers of glucose homeostasis, such as glycated hemoglobin (HbA1c) concentration, fasting and post-glucose load insulin concentrations, and measures of insulin resistance (134). Another meta-analysis of trials that included participants either at-risk of diabetes mellitus or with diabetes mellitus suggested that evidence to support a benefit of magnesium supplementation on measures of insulin resistance was stronger in subjects who were magnesium deficient than in those with normal serum concentrations of magnesium (135). Correcting existing magnesium deficiencies may improve glucose metabolism and insulin sensitivity in subjects with diabetes, but it remains uncertain whether magnesium supplementation can have any therapeutic benefit in patients with adequate magnesium status.

Asthma

The occurrence of hypomagnesemia may be greater in patients with asthma than in individuals without asthma (136). Several clinical trials have examined the effect of intravenous magnesium infusions on acute asthmatic attacks in children or adults who did not respond to initial treatment in the emergency room. Indeed, magnesium can promote bronchodilation in subjects with asthma by interfering with mechanisms like the activation of N-methyl D-aspartate (NMDA) receptors that trigger bronchoconstriction through facilitating calcium influx in airway smooth muscle cells (137). In a meta-analysis of six (quasi) randomized controlled trials in 325 children with acute asthma treated with a short-acting β_2-adrenergic receptor agonist (e.g., salbutamol) and systemic steroids, intravenous magnesium sulfate treatment improved measurements of the respiratory function and reduced the risk of hospital admission by 30% compared to control (138). Another meta-analysis of randomized controlled trials primarily conducted in adults with asthma exacerbations indicated that single infusions of 1.2 to 2 g of magnesium sulfate over 15 to 30 minutes could reduce the risk of hospital admission and improve lung function after initial treatments failed (i.e., oxygen, short-acting β_2 agonist, and steroids) (139).

The use of nebulized, inhaled magnesium for treating asthma has also been investigated. A recent systematic review of 25 randomized controlled trials, including adults, children, or both, found little evidence that inhaled magnesium sulfate alone or along with a β_2-adrenergic receptor agonist and/or a muscarinic anticholinergic (e.g., ipratropium) could improve pulmonary function in patients with acute asthma (140). In addition, oral magnesium supplementation is of no known value in the management of chronic asthma (141-143).

Pain management

The potential analgesic effect of magnesium is attributed in particular to its capacity to block NMDA receptors, which are located in the brain and spinal cord and are involved in pain transduction (144).

Post-operative pain

Several intervention studies have examined the role of magnesium on pain control and analgesic requirement in patients during the immediate post-surgery period.

After cesarean section: Pain management strategies after cesarean section usually involve the injection of an analgesic into either the epidural space (for epidural analgesia) or the subarachnoid space (for spinal [intrathecal] analgesia). A recent meta-analysis of nine randomized controlled trials summarized the evidence regarding the potential use of magnesium sulfate to control or relieve postoperative pain in 827 women who underwent cesarean section (145). All the trials evaluated the effect of a first-line analgesic regimen (i.e., bupivacaine or lidocaine, with or without opioids) with and without the addition of magnesium sulfate. The results suggested that the anesthesia (8 studies) and sensory blockade (6 studies) lasted longer in women who received the additional magnesium sulfate. The use of magnesium sulfate also resulted in lower pain score (3 studies) and in lower postoperative consumption of analgesics (4 studies). Additionally, there was no difference in occurrence of side effects between regimens (145). A recent randomized controlled trial in 60 healthy women undergoing elective cesarean section confirmed that the addition of magnesium sulfate to a bupivacaine/opioid regimen increased the duration of spinal anesthesia and lowered the pain level, yet did not improve the potency of bupivacaine (146). In another study in women with mild preeclampsia who received an epidural injection of ropivacaine after cesarean section, spinal infusion of magnesium sulfate increased the duration of sensory and motor blockade, as well as the time before patients requested an analgesic, compared to midazolam (147).

After a variety of other surgeries: The efficacy of intravenous magnesium has also been examined for local, regional, or systemic pain control following a range of different surgeries. A review of four small randomized controlled studies suggested that, when added to local analgesics, magnesium infusion to patients undergoing tonsillectomy might decrease pain and incidence of laryngospasm, extend the time to first post-operative analgesic requirement, and reduce the number of post-operative analgesic requests (148). Similar observations were reported in two additional meta-analyses, yet there was discrepancy regarding the ability of magnesium to alleviate pain (149, 150). Indeed, the review of eight trials by Xie et al. (150), of which only two scored pain using the same scale, showed no pain reduction with magnesium compared to control. Finally, both meta-analyses reported no reduction in risk of post-operative nausea and vomiting with intravenous magnesium administration (148, 150). A 2018 meta-analysis of four randomized controlled trials in 263 patients also suggested that magnesium sulfate infusion may help reduce pain scores at 2 and 8 hours (but not 24 hours) after laparoscopic cholecystectomy (151). Recent studies have examined the use of magnesium sulfate for pain control after other surgeries, including hysterectomy (152, 153), spinal surgery (154, 155), or during endoscopic sinus (156) or cochlear implantation (157) surgery. Despite conflicting results or reports of limited benefits of magnesium, further research is needed before any conclusions can be drawn.

Neuropathic pain

The effect of magnesium on neuropathic pain has been examined in some clinical studies. The intravenous administration of magnesium sulfate was found to partially or completely alleviate pain in patients with postherpetic neuralgia, a type of neuropathic pain caused by herpes zoster infection (shingles) (158, 159). In a more recent randomized controlled trial in 45 patients with either postherpetic neuralgia or neuropathic pain of traumatic or surgical origin, oral supplementation of magnesium failed to improve measures of pain and quality of life compared to a placebo (160). Another trial is underway to examine the impact of intravenous magnesium with ketamine on neuropathic pain (161).

Migraine headaches

Lower intracellular magnesium concentrations (in both red blood cells and white blood cells) have been reported in individuals who suffer from recurrent migraine headaches compared to migraine-free individuals (162). Additionally, the incidence of hypomagnesemia also appeared to be greater in women who experience migraines with menstruation compared to women without menstrual migraines (163).

A few intervention studies have examined whether an increase in intracellular magnesium concentration with supplemental (oral) magnesium could help decrease the frequency and severity of migraine headaches in affected individuals. Two early placebo-controlled trials demonstrated modest decreases in the frequency of migraine headaches after supplementation with 600 mg/day of magnesium (162, 164). Another placebo-controlled trial in 86 children with frequent migraine headaches found that oral magnesium oxide (9 mg/kg body weight/day) reduced headache frequency over the 16-week intervention (165). However, there was no reduction in the frequency of migraine headaches with 485 mg/day of magnesium in another placebo-controlled study conducted in 69 adults suffering migraine attacks (166). The efficiency of magnesium absorption varies with the type of oral magnesium complex, and this might explain the conflicting results. Although no serious adverse effects were noted during these migraine headache trials, 19 to 40% of individuals taking the magnesium supplements have reported diarrhea and gastric irritation.

The efficacy of magnesium infusions was also investigated in a randomized, single-blind, placebo-controlled, cross-over trial of 30 patients with migraine headaches (167). The administration of 1 gram of intravenous magnesium sulfate ended the attacks, abolished associated symptoms, and prevented recurrence within 24 hours in nearly 90% of the subjects. While this promising result was confirmed in another trial (168), two additional randomized, placebo-controlled studies found that magnesium sulfate was less effective than other molecules (e.g., metoclopramide) in treating migraines (169, 170). The most recent meta-analysis of five randomized, double-blind, controlled trials reported no beneficial effect of magnesium infusion for migraine in adults (171). Another two more recent intervention studies suggested that magnesium sulfate infusion could be more effective and faster than dexamethasone/metoclopramide (172) or caffeine citrate (173) to relieve pain in patients with acute migraine.

The efficacy of magnesium should be examined in larger studies that consider the magnesium status of migraine sufferers (174).

Critical injury or illness

Hypomagnesemia is not uncommon in patients admitted to intensive care units (ICU). Two recent meta-analyses of prospective and retrospective cohort studies reported serum magnesium concentrations ≤0.75 mmol/L in ICU patients at admission or within 24 hours following admission to be associated with a greater need for mechanical ventilation, longer ICU stay, and higher risk of hospital mortality (175, 176). A pooled analysis of three studies also suggested a higher risk of sepsis in ICU patients with hypomagnesemia (175). A recent prospective study conducted in patients admitted with severe head injury found better neurological outcomes after six months in those who presented with normal serum magnesium concentrations at admission compared to those with hypomagnesemia (serum magnesium concentrations <0.65 mmol/L) (177). However, evidence is currently unavailable to suggest that magnesium administration could improve outcomes in critically ill or severely injured patients (178).

Sources

Food sources

The analysis of US national nutrition survey data (NHANES 2003-2006) showed an average magnesium intake in adults (ages ≥19 years) of 278 mg/day when only unfortified food sources were considered (179). Considering all sources of magnesium intakes (i.e., unfortified and fortified food and supplements), the average intake in adults was estimated to be around 330 mg/day — a value close to the estimated average requirements (EAR) for magnesium — suggesting that about one-half of the adult population may be at risk of magnesium inadequacy (179). Yet, the long-term consequences of inadequate dietary intakes remain unclear (1).

Since magnesium is part of chlorophyll, the green pigment in plants, green leafy vegetables are good sources of magnesium. Unrefined grains (whole grains) and nuts also have high magnesium content. Meats and milk have an intermediate content of magnesium, while refined foods generally have the lowest. Water is a variable source of intake; harder water usually has a higher concentration of magnesium salts (2). Some foods that are relatively rich in magnesium are listed in **Table 2**, along with their magnesium content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Magnesium

Food	Serving	Magnesium (mg)
Brazil nuts	1 ounce (6 kernels)	107
Cereal, oat bran	½ cup dry	96
Brown rice, medium-grain, cooked	1 cup	86
Cashews	1 ounce (16 kernels)	83
Fish, mackerel, cooked	3 ounces	82
Spinach, frozen, chopped, cooked	½ cup	78
Almonds	1 ounce (23 kernels)	77
Swiss chard, chopped, cooked	½ cup	75
Lima beans, large, immature seeds, cooked	½ cup	63
Cereal, shredded wheat	2 biscuits	61
Avocado	1 fruit	58
Cereal, all bran (whole wheat)	½ cup, dry	57
Peanuts	1 ounce (28 peanuts)	48
Molasses, blackstrap	1 tablespoon	48
Hazelnuts	1 ounce (21 kernels)	46
Chickpeas, mature seeds, cooked	½ cup	39
Milk, 1% fat	8 fluid ounces	39
Banana	1 medium	32

Supplements

Magnesium supplements are available as magnesium oxide, magnesium hydroxide, magnesium gluconate, magnesium chloride, and magnesium citrate salts, as well as a number of amino acid chelates like magnesium aspartate. Magnesium hydroxide, oxide, or trisilicate salts are used as antacids to mitigate gastric hyperacidity and symptoms of gastroesophageal reflux disease (180).

Safety

Toxicity

Adverse effects have not been identified from magnesium occurring naturally in food. However, adverse effects from excessive magnesium have been observed with intakes of various magnesium salts (i.e., supplemental magnesium) (6). The initial symptom of excess magnesium supplementation is diarrhea — a well-known side effect of magnesium that is used therapeutically as a laxative. Individuals with impaired kidney function are at higher risk for adverse effects of magnesium supplementation, and symptoms of magnesium toxicity have occurred in people with impaired kidney function taking moderate doses of magnesium-containing laxatives or antacids. Elevated serum concentrations of magnesium (hypermagnesemia) may result in a fall in blood pressure (hypotension). Some of the later effects of magnesium toxicity, such as lethargy, confusion, disturbances in normal cardiac rhythm, and deterioration of kidney function, are related to severe hypotension. As hypermagnesemia progresses, muscle weakness and difficulty breathing may occur. Severe hypermagnesemia may result in cardiac arrest (2, 3). The Food and Nutrition Board (FNB) of the US Institute of Medicine set the tolerable upper intake level (UL) for magnesium at 350 mg/day; this UL represents the highest level of daily supplemental magnesium intake likely to pose no risk of diarrhea or gastrointestinal disturbance in almost all individuals. The FNB cautions that individuals with renal impairment are at higher risk for adverse effects from excess supplemental magnesium intake. However, the FNB also notes that there are some conditions that may warrant higher doses of magnesium under medical supervision (2).

Table 3. Tolerable Upper Intake Level (UL) for Supplemental Magnesium

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	65
Children 4-8 years	110
Children 9-13 years	350
Adolescents 14-18 years	350
Adults 19 years and older	350
*Source of intake should be from food and formula only.	

Drug interactions

Magnesium interferes with the absorption of digoxin (a heart medication), nitrofurantoin (an antibiotic), and certain anti-malarial drugs, which could potentially reduce drug efficacy. Bisphosphonates (e.g., alendronate, etidronate), which are drugs used to treat osteoporosis, and magnesium should be taken two hours apart so that the absorption of the bisphosphonates is not inhibited (181, 182). Magnesium has also been found to reduce the efficacy of chlorpromazine (a tranquilizer), penicillamine, oral anticoagulants, and the quinolone and tetracycline classes of antibiotics (181, 182). Intravenous magnesium might inhibit calcium entry into smooth muscle cells and lead to hypotension and muscular weakness if administered with calcium channel blockers (e.g., nifedipin, nicardipin) (182). Because intravenous magnesium has increased the effects of certain muscle-relaxing medications used during anesthesia, it is advisable to let medical staff know if you are taking oral magnesium supplements, laxatives, or antacids prior to surgical procedures. Moreover, long-term use (three months or longer) of proton-pump inhibitors (drugs used to reduce the amount of stomach acid) may increase the risk of hypomagnesemia (183, 184). High doses of furosemide (Lasix) and some thiazide diuretics (e.g., hydrochlorothiazide), if taken for extended periods, may interfere with magnesium reabsorption in the kidneys and result in magnesium depletion (182). Many other medications may also result in renal magnesium loss (3).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the latest RDA for magnesium intake (400 to 420 mg/day for men and 310 to 320 mg/day for women). Despite magnesium being plentiful in foods, it is considered a shortfall nutrient (see the article on Micronutrient Inadequacies in the US Population). Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement might ensure an intake of at least 100 mg/day of magnesium. Few multivitamin/mineral supplements contain more than 100 mg of magnesium due to its bulk. Eating a varied diet that provides green vegetables, whole grains, and nuts daily should provide the rest of an individual's magnesium requirement.

Older adults (>50 years)

Older adults are less likely than younger adults to consume enough magnesium to meet their needs and should therefore take care to eat magnesium-rich foods in addition to taking a multivitamin/mineral supplement daily (see the article on Micronutrient Inadequacies: Subpopulations at Risk). Since older adults are also more likely to have impaired kidney function, they should avoid taking more than 350 mg/day of supplemental magnesium without medical consultation (see Safety).

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Manganese

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Español

Manganese is a mineral element that is both nutritionally essential and potentially toxic. The derivation of its name from the Greek word for magic remains appropriate, because scientists are still working to understand the diverse effects of manganese deficiency and manganese toxicity in living organisms (1).

Function

Manganese (Mn) plays an important role in a number of physiologic processes as a constituent of multiple enzymes and an activator of other enzymes (2).

Antioxidant function

Manganese superoxide dismutase (MnSOD) is the principal antioxidant enzyme in the mitochondria. Because mitochondria consume over 90% of the oxygen used by cells, they are especially vulnerable to oxidative stress. The superoxide radical is one of the reactive oxygen species produced in mitochondria during ATP synthesis. MnSOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, which can be reduced to water by other antioxidant enzymes (3).

Metabolism

A number of manganese-activated enzymes play important roles in the metabolism of carbohydrates, amino acids, and cholesterol (4). Pyruvate carboxylase, a manganese-containing enzyme, and phosphoenolpyruvate carboxykinase (PEPCK), a manganese-activated enzyme, are critical in gluconeogenesis — the production of glucose from non-carbohydrate precursors. Arginase, another manganese-containing enzyme, is required by the liver for the urea cycle, a process that detoxifies ammonia generated during amino acid metabolism (3). In the brain, the manganese-activated enzyme, glutamine synthetase, converts the amino acid glutamate to glutamine. Glutamate is an excitotoxic neurotransmitter and a precursor to an inhibitory neurotransmitter, γ-aminobutyric acid (GABA) (5, 6).

Bone and cartilage formation

Manganese deficiency results in abnormal skeletal development in a number of animal species. Manganese is the preferred cofactor of enzymes called glycosyltransferases; these enzymes are required for the synthesis of proteoglycans that are needed for the formation of healthy cartilage and bone (7).

Wound healing

Wound healing is a complex process that requires increased production of collagen. Manganese is required for the activation of prolidase, an enzyme that functions to provide the amino acid, proline, for collagen formation in human skin cells (8). A genetic disorder known as prolidase deficiency results in abnormal wound healing among other problems and is characterized by abnormal manganese metabolism (7). Glycosaminoglycan synthesis, which requires manganese-activated glycosyltransferases, may also play an important role in wound healing (9).

Nutrient interactions

Iron

Iron and manganese share common absorption and transport proteins, including the divalent metal transporter 1, the lactoferrin receptor, transferrin, and ferroportin (reviewed in 10). Absorption of manganese from a meal decreases as the meal's iron content increases (7). Iron supplementation (60 milligrams [mg]/day for four months) has been associated with decreased blood manganese concentrations and decreased MnSOD activity in leukocytes, indicating a reduction in manganese nutritional status (11).

Additionally, an individual's iron status can affect manganese bioavailability. Intestinal absorption of manganese is increased during iron deficiency and decreased when iron stores are elevated (i.e., high ferritin concentrations) (12). Small studies have found increased blood concentrations of manganese in iron-deficient infants (13) and children (14), and a national survey of adults residing in South Korea found men and women with low ferritin levels had higher blood concentrations of manganese compared to those with normal ferritin levels (15). In this analysis, anemia was associated with higher blood concentrations of manganese in women but not in men (15). Men generally absorb less manganese than women, which may be related to the fact that men usually have higher iron stores than women (16). Iron deficiency has also been shown to increase the risk of manganese accumulation in the brain (17).

Magnesium

Supplemental magnesium (200 mg/day) has been shown to slightly decrease manganese bioavailability in healthy adults, either by decreasing manganese absorption or by increasing its excretion (18).

Calcium

In one set of studies, supplemental calcium (500 mg/day) slightly decreased manganese bioavailability in healthy adults. As a source of calcium, milk had the least effect, while calcium carbonate and calcium phosphate had the greatest effect (18). Several other studies have found minimal effects of supplemental calcium on manganese metabolism (19).

Regulation

Although manganese is a nutritionally essential mineral, it is potentially toxic; thus, it is important for the body to tightly regulate manganese homeostasis. While the exact mechanisms that govern manganese homeostasis are not completely understood, systemic regulation is achieved through intestinal control of manganese absorption and hepatic excretion of manganese into bile (20). At the cellular level, influx of manganese into cells is regulated by several different transport proteins, including the transferrin receptor, the divalent metal transporter 1 (DMT 1), zinc-interacting proteins 8 and 14 (ZIP8 and ZIP14), as well as others (reviewed in 21). Efflux of manganese from cells is accomplished by various transporters, including SLC30A10; the sodium-calcium exchanger; and the iron transporter, ferroportin (reviewed in 22). Moreover, subcellular organelles (i.e., the nucleus, mitochondria, Golgi apparatus, lysosome, endosome) utilize various transporters for manganese trafficking within the cell, but the exact mechanisms of regulation are not fully understood (21).

Deficiency

Manganese deficiency has been observed in a number of animal species, but manganese deficiency is not a concern in humans. Signs of manganese deficiency vary among animal species and may include impaired growth, impaired reproductive function, skeletal abnormalities, impaired glucose tolerance, and altered carbohydrate and lipid metabolism. In humans, demonstration of a manganese deficiency syndrome has been less clear (2, 7). A child on long-term total parenteral nutrition (TPN) lacking manganese developed bone demineralization and impaired growth that were corrected by manganese supplementation (23). Young men who were fed a low-manganese diet developed decreased serum cholesterol concentrations and a transient skin rash (24). Blood concentrations of calcium, phosphorus, and alkaline phosphatase were also elevated, which may indicate increased bone remodeling as a consequence of insufficient dietary manganese. Young women fed a manganese-poor diet developed mildly abnormal glucose tolerance in response to an intravenous (IV) infusion of glucose (19). Overall, manganese deficiency is quite rare, and there is more concern for toxicity related to manganese overexposure (see Safety).

The Adequate Intake (AI)

Because there was insufficient information on manganese requirements to set a Recommended Dietary Allowance (RDA), the Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) set an adequate intake (AI). Since overt manganese deficiency has not been documented in humans eating natural diets, the FNB based the AI on average dietary intakes of manganese determined by the Total Diet Study — an annual survey of the mineral content of representative American diets (4). AI values for manganese are listed in **Table 1** in milligrams (mg)/day by age and gender. Manganese requirements are increased in pregnancy and lactation (4).

Table 1. Adequate Intake (AI) for Manganese

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.003	0.003
Infants	7-12 months	0.6	0.6
Children	1-3 years	1.2	1.2
Children	4-8 years	1.5	1.5
Children	9-13 years	1.9	1.6
Adolescents	14-18 years	2.2	1.6
Adults	19 years and older	2.3	1.8
Pregnancy	all ages	-	2.0
Breast-feeding	all ages	-	2.6

Disease Prevention

Low dietary manganese intake or low levels of manganese in blood or tissue have been associated with various chronic diseases. Although manganese insufficiency is not currently thought to cause the diseases discussed below, more research may be warranted to determine whether suboptimal manganese nutritional status contributes to certain disease processes.

Osteoporosis

Early studies found women with osteoporosis had decreased plasma or serum concentrations of manganese and an enhanced plasma response to an oral dose of manganese (25, 26), suggesting they may have lower manganese status than women without osteoporosis. However, more recent studies in postmenopausal women have reported conflicting results, with one study finding lower blood manganese concentrations among women with osteoporosis compared to those without osteoporosis (27) and another finding no differences (28). A study in healthy postmenopausal women found that a supplement containing manganese (5 mg/day), copper (2.5 mg/day), and zinc (15 mg/day) in combination with a calcium supplement (1,000 mg/day) was more effective than the calcium supplement alone in preventing spinal bone loss over a two-year period (29). However, the presence of other trace elements in the supplement makes it impossible to determine whether manganese supplementation was the beneficial agent for maintaining bone mineral density.

Diabetes mellitus

In animal models, manganese deficiency results in impaired insulin secretion and glucose intolerance similar to diabetes mellitus (30); however, results of human studies on manganese and type 2 diabetes have been somewhat conflicting. Manganese intake was inversely associated with type 2 diabetes in 71,270 French women participating in the E3N-EPIC cohort study (31). In an analysis of two prospective cohorts of Chinese adults (ages 20-74 years at baseline), followed for a mean of 4.2 and 5.3 years, higher dietary intakes of manganese were associated with a lower risk of type 2 diabetes; these associations were independent of dietary total antioxidant capacity, a measure of dietary antioxidant intake (32). Most recently, a prospective cohort study of 19,862 adults (ages 40-79 at baseline) participating in the Japan Collaborative Cohort Study, followed for five years, found higher dietary intake of manganese to be associated with a lower risk of type 2 diabetes in women but not in men (33).

While these studies of dietary manganese intake are suggestive of a protective association with type 2 diabetes, studies employing biomarkers of manganese intake – either blood concentrations of manganese or urinary manganese excretion — have reported mixed results. Most studies conducted have been small case-control studies; studies to date have reported blood manganese concentrations in patients with diabetes were higher (34-36), lower (37), or similar (38-40) compared to blood manganese concentrations in controls without diabetes. Additionally, a case-control study that included 3,228 adults in China reported a U-shaped relationship between plasma concentration of manganese and type 2 diabetes, meaning those with low or high blood concentrations had a higher odds of diabetes when compared to those with an intermediate blood concentration of manganese (41). In a cross-sectional analysis of adults participating in the Korean National Health and Nutrition Examination Survey, blood concentrations of manganese were significantly lower among those with diabetes compared to those without diabetes (42). Further, one case-control study found higher urinary manganese excretion in patients with diabetes compared to controls without diabetes (37). Results of case-control studies are more likely to be distorted by bias (i.e., the selection bias with the selection of cases and controls, as well as dietary recall bias) than results of prospective cohort studies.

Moreover, one study of functional manganese status found the activity of the antioxidant enzyme, MnSOD, to be lower in the white blood cells of patients with diabetes than in those without diabetes (43). When given at the same time as an oral glucose challenge, an acute oral dose of 15 mg or 30 mg manganese did not improve glucose tolerance in subjects with diabetes or in controls without diabetes (44).

Although manganese appears to play a role in glucose metabolism, it is not clear whether higher manganese status might improve glucose tolerance and protect against the development of type 2 diabetes mellitus.

Epilepsy (seizure disorders)

Manganese deficient rats are more susceptible to seizures than manganese sufficient rats, and rats that are genetically prone to epilepsy have lower than normal brain and blood manganese concentrations. Certain subgroups of humans with epilepsy reportedly have lower whole blood manganese concentrations than control subjects without epilepsy (45). One study found blood manganese concentrations of individuals with epilepsy of unknown origin were lower than those of individuals whose epilepsy was induced by trauma (e.g., head injury) or disease (46), suggesting a possible genetic relationship between epilepsy and abnormal manganese metabolism. While manganese deficiency does not appear to be a cause of epilepsy in humans, the relationship between manganese metabolism and epilepsy deserves further research (7, 45, 47).

Sources

Food sources

In the US, estimated average intakes of dietary manganese range from 2.1 to 2.3 mg/day for men and 1.6 to 1.8 mg/day for women (4). Surveys have found those adhering to a vegetarian diet have manganese intakes of up to 7.0 mg/day (reviewed in 48). Rich sources of manganese include whole grains, legumes, nuts, leafy vegetables, and teas (49). Foods high in phytic acid, such as beans, seeds, nuts, whole grains, and soy products, or foods high in oxalic acid, such as cabbage, spinach, and sweet potatoes, may slightly inhibit manganese absorption. Although teas are rich sources of manganese, the tannins present in tea may moderately reduce the absorption of manganese (18). Intakes of other minerals, including iron, calcium, and phosphorus, have been found to limit retention of manganese (4). The manganese content of some manganese-rich foods is listed in milligrams (mg) in **Table 2**. For more information on the nutrient content of foods, search USDA's FoodData Central database (50).

Table 2. Some Food Sources of Manganese

Food	Serving	Manganese (mg)
Pineapple, raw	½ cup, chunks	0.77
Pineapple juice	½ cup (4 fl. oz.)	0.63
Pecans	1 ounce (19 halves)	1.28
Almonds	1 ounce (23 whole kernels)	0.62
Peanuts	1 ounce	0.55
Peanut butter, smooth style, no salt	2 tablespoons	0.53
Instant oatmeal (prepared with water)	1 packet	0.99
Raisin bran cereal	1 cup	0.78-3.02
Brown rice, long-grain, cooked	½ cup	0.99
Whole-wheat bread	1 slice	0.70
Pinto beans, cooked	½ cup	0.39
Lima beans, cooked	½ cup	0.49
Navy beans, cooked	½ cup	0.48
Spinach, cooked	½ cup	0.84
Sweet potato, cooked	½ cup, mashed	0.44
Tea (green)	1 cup (8 ounces)	0.41-1.58
Tea (black)	1 cup (8 ounces)	0.18-0.77

Breast milk and infant formulas

Infants are exposed to varying amounts of manganese depending on their source of nutrition. Manganese concentrations in breast milk, cow-based formula, and soy-based formula range from 3 to 10 micrograms/liter (μg/L), 30 to 50 μg/L, and 200 to 300 μg/L, respectively. However, the bioavailability of manganese from breast milk is higher than from infant formulas, and manganese deficiencies in breast-fed infants or toxicities in formula-fed infants have not been reported (20).

Water

Manganese concentrations in drinking water range from 1 to 100 micrograms (μg)/L, but most sources contain less than 10 μg/L (51). The US Environmental Protection Agency (EPA) recommends 0.05 mg (50 μg)/L as the maximum allowable manganese concentration in drinking water (52).

Supplements

Several forms of manganese are found in supplements, including manganese gluconate, manganese sulfate, manganese ascorbate, and amino acid chelates of manganese. Manganese is available as a stand-alone supplement or in combination products (53). Relatively high levels of manganese ascorbate may be found in a bone/joint health product containing chondroitin sulfate and glucosamine hydrochloride (see Safety).

Parenteral nutrition

Manganese may be present in solutions of parenteral nutrition either included as a trace element or as an incidental contaminant (see Intravenous manganese in the Safety section) (54, 55).

Safety

Toxicity

Inherited manganese-overload disorders

Autosomal recessive mutations in the *SLC30A10* gene, which encodes a manganese transporter expressed in the liver and brain, causes a manganese overload syndrome. Such loss-of-function mutations lead to manganese accumulation in certain brain regions and in the liver, causing hypermanganesemia, dystonia parkinsonism, and hepatic dysfunction at an early age (56, 57). Autosomal recessive mutations in the *SLC39A14* gene have also been reported, leading to hypermanganesemia and similar a neurological phenotype, but liver disease is absent with this specific mutation (58). Chelation therapy is important to treat these inherited manganese-overload disorders (59).

Inhaled manganese

Manganese toxicity may result in multiple neurologic problems and is a well-recognized health hazard for people who inhale manganese dust, such as welders, miners, and smelters (1, 4). Unlike ingested manganese, inhaled manganese is transported directly to the brain before it can be metabolized in the liver (60, 61). The symptoms of manganese toxicity generally appear slowly over a period of months to years. In its worst form, manganese toxicity can result in a permanent neurological disorder with symptoms similar to those of Parkinson's disease, including tremors, difficulty walking, and facial muscle spasms. This syndrome, often called manganism, is sometimes preceded by psychiatric symptoms, such as irritability, aggressiveness, and even hallucinations (62, 63). Additionally, environmental or occupational inhalation of manganese can cause an inflammatory response in the lungs (64), with clinical symptoms including cough, acute bronchitis, and decreased lung function (65).

Methylcyclopentadienyl manganese tricarbonyl (MMT)

Methylcyclopentadienyl manganese tricarbonyl (MMT) is a manganese-containing compound used in gasoline as an anti-knock additive. Although it has been used for this purpose in Canada for more than 20 years, uncertainty about adverse health effects from inhaled exhaust emissions kept the US EPA from approving its use in unleaded gasoline. In 1995, a US court decision made MMT available for widespread use in unleaded gasoline (60). A study in Montreal, where MMT had been used for more than 10 years, found airborne manganese levels to be similar to those in areas where MMT was not used (66). Another Canadian study found higher concentrations of respirable manganese in an urban versus a rural area, but average concentrations in both areas were below the safe level set by the US EPA (67). The impact of long-term exposure to low levels of MMT combustion products, however, has not been thoroughly evaluated and will require additional study (68).

A single case of reversible neurotoxicity and seizures following unintentional MMT ingestion has been documented: a 54-year old man accidentally drank an MMT-containing anti-knock agent that he assumed was an energy drink due so similar product labeling (69).

Ingested manganese

Limited evidence suggests that high manganese intakes from drinking water may be associated with neurological symptoms similar to those of Parkinson's disease. Severe neurological symptoms were reported in 25 people who drank water contaminated with manganese — and probably other contaminants — from dry cell batteries for two to three months (70). Water manganese concentrations were found to be 14 mg/L almost two months after symptoms began and may have already been declining (1). A study of older adults in Greece found a high prevalence of neurological symptoms in those exposed to water manganese levels of 1.8 to 2.3 mg/L (71), while a study in Germany found no evidence of increased neurological symptoms in people drinking water with manganese levels ranging from 0.3 to 2.2 mg/L compared to those drinking water containing less than 0.05 mg/L of manganese (72). Manganese in drinking water may be more bioavailable than manganese in food. However, none of the studies measured dietary manganese, so total manganese intake in these cases is unknown. In the US, the EPA recommends 0.05 mg/L as the maximum allowable manganese concentration in drinking water (52), but the World Health Organization does not currently have a health-based limit for manganese in drinking water (73, 74).

Additionally, several cross-sectional studies have associated high levels of manganese in drinking water with cognitive and behavioral deficits in children (reviewed in 75). For example, a cross-sectional study of 362 children (ages 6-13 years) in Canada found children with the highest manganese concentrations in home tap water (median of 216 μg/L) had a 6.2-point lower Full Scale IQ (lower Performance IQ but not Verbal IQ) than those with lowest manganese levels in home tap water (median of 1 μg/L) (76). A cohort study that followed 287 of these children for a mean of 4.4 years found that exposure to higher concentrations of manganese in drinking water was linked to a lower Performance IQ among girls but a higher Performance IQ among boys (77). Additionally, a prospective cohort study among 1,265 children in Bangladesh did not find manganese concentration in drinking water (medians of 0.20 mg/L during pregnancy and 0.34 mg/L at 10 years) to be associated with any measure of cognitive ability (i.e., IQ, verbal comprehension, perceptual reasoning, working memory, processing speed) when assessed at age 10 (78). Yet, this study associated manganese in drinking water with higher risks of conduct problems among boys and low prosocial scores among girls (78). In a population-based cohort study in Denmark that followed 643,401 children, exposure to higher manganese concentrations in drinking water was linked to a heightened risk of one subtype of attention-deficit hyperactive disorder (79). Specifically, exposure to a manganese concentration in drinking water of at least 100 μg/L was associated with a 51% higher risk of the ADHD-Inattentive subtype in girls and a 20% higher risk in boys, in comparison to exposure of <5 μg/L — using these exposure comparisons, a 9% increased risk of ADHD-Overall was observed in girls and no difference found in boys (79).

Only a few adverse effects of manganese intake from supplements have been documented. A single case of manganese toxicity was reported in a person who took large amounts of mineral supplements for years (51), while another case was reported as a result of a person taking a Chinese herbal supplement (62). More recently, Parkinson's disease was reported in a woman taking 100 mg/day of manganese chloride for at least two years, followed by 30 mg/day for two months (80).

Manganese toxicity resulting from food alone has not been reported in humans, even though certain vegetarian diets could provide up to 20 mg/day of manganese (4, 51).

Intravenous manganese

Manganese neurotoxicity has been observed in individuals receiving total parenteral nutrition (TPN), both as a result of excessive manganese in the solution and as an incidental contaminant (54). Neonates are especially vulnerable to manganese-related neurotoxicity (81). Infants receiving manganese-containing TPN can be exposed to manganese concentrations about 100-fold higher than breast-fed infants (20). Because of potential toxicities, some argue against including manganese in parenteral nutrition (82).

Individuals with increased susceptibility to manganese toxicity

- **Chronic liver disease:** Manganese is eliminated from the body mainly in bile. Thus, impaired liver function may lead to decreased manganese excretion. Manganese accumulation in individuals with cirrhosis or liver failure may contribute to neurological problems and Parkinson's disease-like symptoms (1, 53).
- **Infants and children:** Compared to adults, infants and children have higher intestinal absorption of manganese, as well as lower biliary excretion of manganese (83). Thus, infants and children are especially susceptible to any negative, neurotoxic effects of manganese. Indeed, several studies in school-aged children have reported deleterious cognitive and behavioral effects following excessive manganese exposure (76, 84-90). Additional studies have associated higher manganese exposures during pregnancy with cognitive and motor deficits in children under six years of age (reviewed in 75).
- **Iron-deficient populations:** Iron deficiency has been shown to increase the risk of manganese accumulation in the brain (17).
- **Individuals with occupational exposures to airborne manganese**, such as welders, miners, and smelters (reviewed in 21).
- **Abusers of the illicit drug, methcathinone (ephedrone):** Intravenous use of manganese-contaminated methcathinone (i.e., when the drug is synthesized with potassium permanganate as the oxidant) can cause lasting neurological damage and a parkinsonism disorder (91, 92).

Due to the severe implications of manganese neurotoxicity, the Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) set very conservative tolerable upper intake levels (UL) for manganese; the ULs are listed in **Table 3** according to age (4).

Table 3. Tolerable Upper Intake Level (UL) for Manganese

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	2
Children 4-8 years	3
Children 9-13 years	6
Adolescents 14-18 years	9
Adults 19 years and older	11
*Source of intake should be from food and formula only.	

Drug interactions

Magnesium-containing antacids and laxatives and the antibiotic medication, tetracycline, may decrease the absorption of manganese if taken together with manganese-containing foods or supplements (53).

High levels of manganese in supplements marketed for bone/joint health

Two studies have found that supplements containing a combination of glucosamine hydrochloride, chondroitin sulfate, and manganese ascorbate are beneficial in relieving pain due to mild or moderate osteoarthritis of the knee when compared to a placebo (93, 94). The dose of elemental manganese supplied by the supplements was 30 mg/day for eight weeks in one study (94) and 40 mg/day for six months in the other study (93). No adverse effects were reported during either study, and blood manganese concentrations were not measured. Neither study compared the treatment containing manganese ascorbate to a treatment containing glucosamine hydrochloride and chondroitin sulfate without manganese ascorbate, so it is impossible to determine whether the supplement would have resulted in the same benefit without high doses of manganese.

Linus Pauling Institute Recommendation

The adequate intake (AI) for manganese (2.3 mg/day for adult men and 1.8 mg/day for adult women) appears sufficient to prevent deficiency in most individuals. The daily intake of manganese most likely to promote optimum health is not known. Following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement containing 100% of the daily values (DV) of most nutrients will generally provide 2.3 mg/day of manganese. Because of the potential for toxicity and the lack of information regarding benefit, manganese supplementation beyond 100% of the DV (2.3 mg/day) is not recommended. There is presently no evidence that the consumption of a manganese-rich plant-based diet results in manganese toxicity.

Older adults (>50 years)

The requirement for manganese is not known to be higher for older adults. However, liver disease is more common in older adults and may increase the risk of manganese toxicity by decreasing the elimination of manganese from the body (see Toxicity). Manganese supplementation beyond 100% of the DV (2.3 mg/day) is not recommended.

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Molybdenum

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Español

Summary

- The molybdenum atom is part of the molybdenum cofactor in the active site of four enzymes in humans: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime reducing component. *(More information)*
- Excess molybdenum intake causes fatal copper deficiency diseases in grazing animals. Their rumen is the site of high sulfide generation, and the interaction of molybdenum with sulfur results in the formation of thiomolybdates. Tetrathiomolybdate, a thiomolybdate with four sulfur atoms, can form complexes with copper preventing its absorption and blocking the activity of copper-dependent enzymes. *(More information)*
- In humans, tetrathiomolybdate therapy has been developed for Wilson's disease, a genetic disease in which the accumulation of copper in tissues leads to liver and brain damage. More recently, tetrathiomolybdate use has been explored for the treatment of cancer and inflammatory diseases. *(More information)*
- Mutations in the molybdenum cofactor biosynthetic pathway lead to the combined deficiency of all molybdenum-dependent enzymes. Molybdenum cofactor deficiency Type A is due to mutations in the *MOCS1* gene, while Type B deficiency is caused by mutations in *MOCS2*. Both Type A and Type B deficiencies result in the loss of sulfite oxidase activity, also observed in isolated sulfite oxidase deficiency and characterized by severe neurologic abnormalities in affected patients. *(More information)*
- A new treatment option for molybdenum cofactor deficiency Type A is now available in the US. Intravenous administration of a replacement drug for cyclic pyranopterin monophosphate may help correct the metabolic disorder and prevent neurologic deterioration in patients with Type A deficiency. Patients with Type B deficiency do not lack this molecule and therefore cannot benefit from this treatment. However, one study showed that pyridoxine supplementation in these patients could alleviate suffering by abolishing seizures. *(More information)*
- The molybdenum content of foods depends on the molybdenum content of soils, which can vary considerably. Variation in esophageal cancer incidence worldwide has been linked to the molybdenum content in soils and food. Similar observations have been made in order to identify the factors associated with a population's extended lifespan. *(More information)*

Molybdenum is an essential trace element for virtually all life forms. It functions as a cofactor for a number of enzymes that catalyze important chemical transformations in the global carbon, nitrogen, and sulfur cycles (1). Thus, molybdenum-dependent enzymes are not only required for human health, but also for the health of our ecosystem.

Function

The biological form of the molybdenum atom is an organic molecule known as the molybdenum cofactor (Moco) present in the active site of Moco-containing enzymes (molybdoenzymes) (2). In humans, molybdenum is known to function as a cofactor for four enzymes (3):

In humans, molybdenum is known to function as a cofactor for four enzymes (3).

- **Sulfite oxidase** catalyzes the transformation of sulfite to sulfate, a reaction that is necessary for the metabolism of sulfur-containing amino acids (methionine and cysteine). Recent evidence also indicates a role for sulfite oxidase in the reduction of nitrite to nitric oxide (4).
- **Xanthine oxidase** catalyzes the breakdown of nucleotides (precursors to DNA and RNA) to form uric acid, which contributes to the plasma antioxidant capacity of the blood.
- **Aldehyde oxidase** and xanthine oxidase catalyze hydroxylation reactions that involve a number of different molecules with similar chemical structures. Xanthine oxidase and aldehyde oxidase also play a role in the metabolism of drugs and toxins (5).
- **Mitochondrial amidoxime reducing component (mARC)** was described fairly recently (6), and its precise function is still under investigation. Initial studies showed that mARC forms a three-component enzyme system with cytochrome *b*5 and NADH/cytochrome *b*5 reductase that catalyzes the detoxification of mutagenic *N*-hydroxylated bases (7). mARC reduces various *N*-hydroxylated compounds and plays an important role in prodrug metabolism (8, 9). Moreover, recent studies have found a separate function of this enzyme system: the reduction of nitrite to nitric oxide (10). Two isoforms of the mARC enzyme are known to exist in humans, mARC1 and mARC2 (11).

Of these enzymes, sulfite oxidase is known to be crucial for human health (12). Hereditary xanthinuria, characterized by a deficiency in xanthine oxidase (Type I) or by a deficiency in both xanthine oxidase and aldehyde oxidase (Type II), can be asymptomatic. However, in less than half of the cases, affected individuals exhibit a range of health issues of variable severity (13, 14).

Nutrient interactions

Copper

An early study reported that molybdenum intakes of 500 μg/day and 1,500 μg/day from sorghum increased urinary copper excretion (2). However, the results of a more recent, well-controlled study indicated that very high dietary molybdenum intakes (up to 1,500 μg/day) did not adversely affect copper nutritional status in eight, healthy young men (15).

Tetrathiomolybdate

Excess dietary molybdenum has been found to result in copper deficiency in grazing animals (ruminants). In the digestive tract of ruminants, the formation of compounds containing sulfur and molybdenum, known as thiomolybdates, prevents the absorption of copper and can cause fatal copper-dependent disorders (16, 17). Tetrathiomolybdate (TM) is a molecule that can form high-affinity complexes with copper, controlling free copper (copper that is not bound to ceruloplasmin), and inhibiting copper chaperones and copper-containing enzymes (18, 19). TM's ability to lower free copper levels is exploited in the treatment of Wilson's disease, a genetic disorder characterized by copper accumulation in tissues responsible for hepatic and neurologic disorders. Neurologic worsening has been linked with toxic levels of free copper in the serum of neurologically presenting patients. TM therapy seems able to stabilize neurologic status and prevent neurologic deterioration in these patients, as opposed to the standard initial treatment of choice (20).

Copper is also a required cofactor for enzymes involved in inflammation and angiogenesis that are known to accelerate cancer progression and metastasis. Copper depletion studies employing TM have been initiated in patients with advanced malignancies with the aim of preventing disease progression or relapse. These pilot trials showed promising results in individuals with metastatic kidney cancer (21), metastatic colorectal cancer (22), and breast cancer with high risk of relapse (23). TM was relatively well-tolerated and stabilized disease or prevented relapse in correlation with copper depletion. TM's efficacy has also been investigated in animal models of inflammatory and immune-related diseases (24, 25), but clinical studies are needed to evaluate whether copper depletion might stabilize diseases and improve survival in humans, as suggested by a trial of TM therapy with patients with biliary cirrhosis (26).

Deficiency

Dietary molybdenum deficiency has never been observed in healthy people (2).

Acquired molybdenum deficiency

The only documented case of acquired molybdenum deficiency occurred in a patient with Crohn's disease on long-term total parenteral nutrition (TPN) without molybdenum added to the TPN solution (27). The patient developed rapid heart and respiratory rates, headaches, and night blindness, and ultimately became comatose. The patient was diagnosed with defects in uric acid production and sulfur amino acid metabolism. The patient's clinical condition improved and the amino acid intolerance disappeared when the TPN solution was discontinued and instead supplemented with molybdenum in the form of ammonium molybdate (300 μg/day) (27).

Inherited molybdenum cofactor deficiency

Because molybdenum functions only in the form of the Moco in humans, any disturbance of Moco metabolism can disrupt the function of all molybdoenzymes. Current understanding of the essentiality of molybdenum in humans is based largely on the study of individuals with very rare inborn metabolic disorders caused by a deficiency in Moco. Moco is synthesized *de novo* by a multistep metabolic pathway involving four genes: *MOCS1*, *MOCS2*, *MOCS3*, and *GPHN* (see **Figure 1** below). To date, more than 60 mutations affecting mostly *MOCS1* and *MOCS2* have been identified (28).

The absence of a functional Moco has a direct impact on the activity of the molybdoenzymes. Metabolic disorders specifically associated with deficiency in sulfite oxidase activity include an accumulation of sulfite, taurine, S-sulfocysteine, and thiosulfate (see **Figure 2** below). This metabolic profile is identical to that observed in isolated sulfite oxidase deficiency (ISOD), an inherited condition caused by mutations in the *SUOX* gene that codes for sulfite oxidase (29). Compared with ISOD, Moco deficiency (MocoD) also affects the xanthine pathway and leads to an accumulation of hypoxanthine and xanthine, and low to undetectable uric acid concentrations in blood (see **Figure 3** below). MocoD and ISOD have been diagnosed in more than 100 individuals worldwide. However the global prevalence of MocoD is likely to be underestimated as a result of a failure to diagnose or to report (28, 30, 31). The incidence of MocoD has been recently estimated at one in 100,000 to 200,000 live births (32).

Both MocoD and ISOD result from recessive traits, meaning that only individuals who inherit two copies of the abnormal gene (one from each parent) develop the disease. Individuals who inherit only one copy of the abnormal gene are known as carriers of the trait but do not exhibit any symptoms. ISOD and MocoD can be diagnosed relatively early in pregnancy (10-14 weeks' gestation) by enzyme activity assays using amniotic cell and chorionic villus sampling and by genetic testing (30, 33). These disorders typically occur in the first days of life, although a few cases of MocoD with late presentation have been described (34-37). The loss of sulfite oxidase activity in ISOD and MocoD leads to severe neurological dysfunction characterized by cerebral atrophy, mental retardation, intractable seizures, and dislocation of ocular lenses. At present, it is not clear whether the neurologic effects are a result of the accumulation of a toxic metabolite, such as sulfite, or inadequate sulfate production. Patients with ISOD and MocoD were also found with elevated excretion of α-amino adipic semialdehyde (α-AASA) (38). α-AASA accumulation is the metabolic signature of a deficiency in α-AASA dehydrogenase observed in patients with pyridoxine-dependent epilepsy. The enzymatic deficiency in these individuals causes an increase in α-AASA and its cyclic form piperideine-6-carboxylate (P6C). P6C can trap pyridoxal-5-phosphate (PLP), the active form of vitamin B_6 (pyridoxine), leading to a deficiency in PLP, which is corrected with supplemental pyridoxine. A decrease in PLP has also been observed in the cerebrospinal fluid from ISOD and MocoD patients (39). It is not clear whether sulfite is responsible for the accumulation of α-AASA and the deficiency in PLP in ISOD and MocoD patients. Nevertheless, pyridoxine and folic acid supplementation in patients with MocoD successfully normalized the PLP level and abolished seizures in two patients with mutations in *MOCS2* (MocoD Type B) (40). Although anti-seizure medications and dietary restriction of sulfur-containing amino acids may be beneficial in some cases (41), there are no treatment options for patients with mutations in the *MOCS2*, *GPHN* (MocoD Type C), or *SUOX* genes. Pyridoxine supplementation is an option being considered to alleviate specific clinical features in patients.

A successful treatment using cyclic pyranopterin monophosphate (cPMP) has been described for patients with mutations in the *MOCS1* gene (i.e., those with MocoD Type A) (42). The *MOCS1* gene controls the initial step in the Moco biosynthetic pathway, catalyzing the conversion of guanosine triphosphate into cPMP. Therefore, patients with mutations in the *MOCS1* gene lack cPMP. Daily administration of cPMP to patients resolved all metabolic abnormalities associated with defective sulfite oxidase and xanthine pathways and prevented further signs of neurologic deterioration (43, 44). Early diagnosis and initiation of treatment are essential to ensure success (44). A prospective cohort study of 16 young infants, followed for five years, found that intravenous cPMP treatment was associated with clinical improvement in most infants with MocoD Type A but not in those with MocoD Type B (42). The US Food and Drug Administration recently approved the cPMP replacement drug, fosdenopterin (brand name: Nulibry), for intravenous treatment of MocoD Type A (45). Since cPMP replacement therapy can only benefit MocoD Type A, additional treatment methods are required. A mouse model for MocoD Type B has been recently developed, which may aid in the development of a therapy for those suffering from the *MOSC2* mutation (46).

Figure 1. Molybdenum Cofactor Biosynthesis

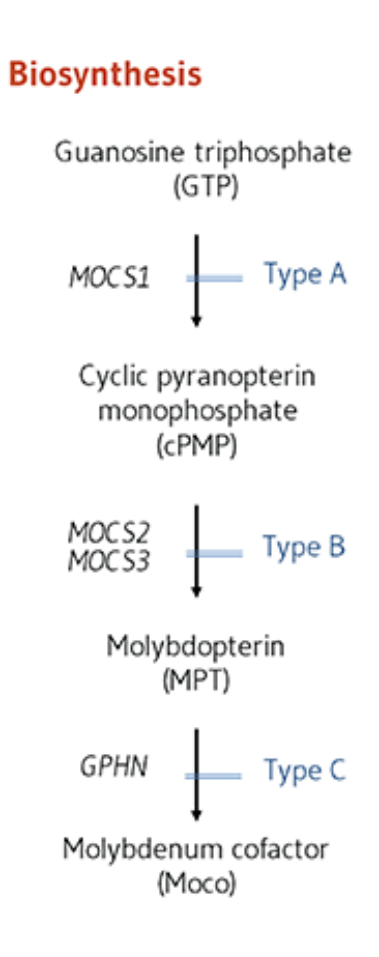

Guanosine triphosphate (GTP)
MOCS1
Type A
Cyclic pyranopterin monophosphate (cPMP)
MOCS2
MOCS3
Type B
Molybdopterin (MPT)
GPHN
Type C
Molybdenum cofactor (Moco)

Figure 2. Sulfur Amino Acid Metabolism

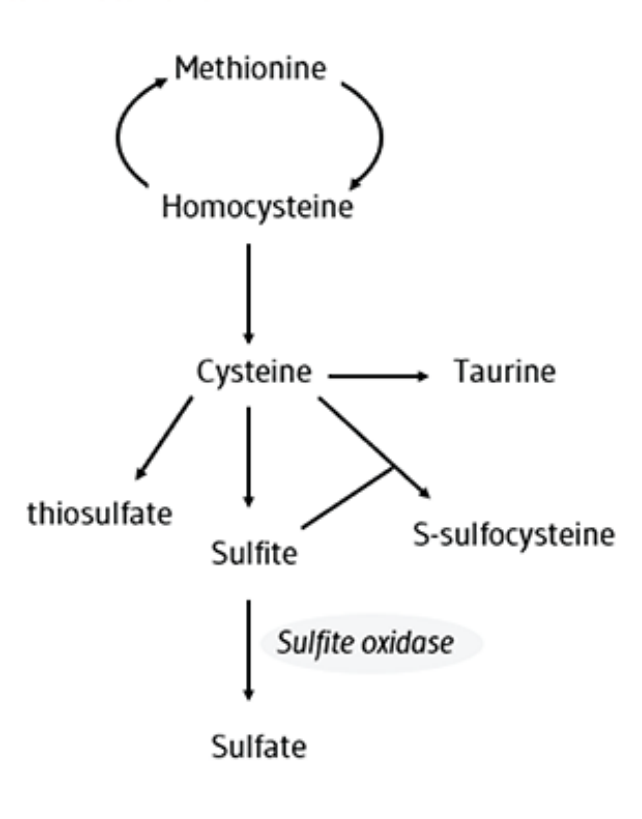
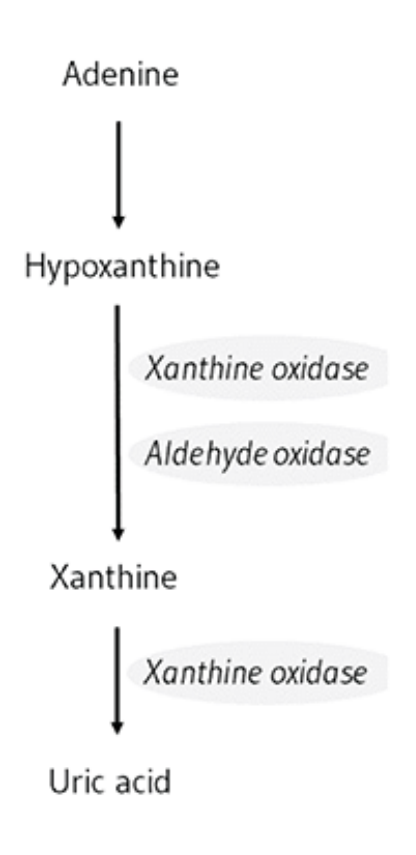


Figure 3. Uric Acid Production



The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for molybdenum was most recently revised in January 2001 by the Food and Nutrition Board of the Institute of Medicine (now the National Academy of Medicine) (2). It was based on the results of nutritional balance studies conducted in eight, healthy young men under controlled laboratory conditions (47, 48). The RDA values for molybdenum are listed in **Table 1** in micrograms (μg)/day by age and gender. Adequate intake (AI) levels were set for infants based on mean molybdenum intake from human milk, exclusively. The Daily Value (DV), derived from the RDA, is 45 μg/day for individuals 4 years of age or older (49).

Table 1. Recommended Dietary Allowance (RDA) for Molybdenum

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	3 (AI)	3 (AI)
Children	1-3 years	17	17
Children	4-8 years	22	22
Children	9-13 years	34	34
Adolescents	14-18 years	43	43
Adults	19 years and older	45	45
Pregnancy	all ages	-	50
Breast-feeding	all ages	-	50

Disease Prevention

Esophageal cancer

Linxian is a small region in northern China where the incidence of cancer of the esophagus and stomach is very high (10 times higher than the average in China and 100 times higher than the average in the US). The soil in this region is low in molybdenum and other mineral elements; therefore, dietary molybdenum intake is also low. Studies conducted in other areas of low and high incidence of esophageal cancer showed that content of molybdenum and zinc in hair and nails is significantly lower in inhabitants of high-risk regions compared to cold spots. Moreover, esophageal cancer patients display reduced content of the trace elements compared to healthy relatives (50, 51).

Increased intake of nitrosamines, which are known carcinogens, may be one of a number of dietary and environmental factors that contributes to the development of esophageal cancer in residents of high-risk regions. Adding ammonium molybdate to the soil may help decrease the risk of esophageal cancer by limiting nitrosamine exposure. It is not clear whether dietary molybdenum supplementation is beneficial in decreasing the risk of esophageal cancer. A placebo-controlled, intervention trial conducted in the Linxian area found that supplementation with molybdenum (30 μg/day) and vitamin C (120 mg/day) for 5.25 years did not decrease the incidence or mortality from esophageal cancer (52-54). The 25-year follow-up of this trial found that co-supplementation with these two micronutrients actually led to small increases in risk of death from gastric cardia cancer and cancer in general, but not death from esophageal cancer (54). However, a subanalysis of this 25-year follow-up revealed that co-supplementation with molybdenum and vitamin C slightly increased risk of mortality from esophageal cancer in those who were 55 years or older when the trial initially began (HR, 1.16; 95% CI: 1.04-1.30) (54).

Longevity

Rugao is a county in Jiangsu province (China) renowned for the longevity of its residents. Extended longevity can hardly be attributed to significant differences in traditions, lifestyles, or dietary habits among the residents, and most longevous people are not related to one another, limiting the possible influence of genetics. However, the county has a large number of different soils whose compositions could affect the distribution of trace elements in water and crops and ultimately be linked with human health and longevity. Significant correlations were found between the ratio of people over 90 years old per 100,000 inhabitants and trace elements, including molybdenum, in soils, drinking water, and rice, which constitute key elements of their natural environment (55). The percentage of long-lived people (>80 years old) in Zhongxiang (Hubei province) was also positively linked to the content of molybdenum in their staple food, rice (56). In these regions, it is likely that combinations of trace elements contribute to optimum health and longevity as opposed to the sole effect of molybdenum.

Sources

Food sources

The Total Diet Study, an annual survey of the mineral content in the typical American diet, indicates that the dietary intake of molybdenum averages 76 μg/day for women and 109 μg/day for men. Thus, usual molybdenum intakes are well above the RDA for molybdenum. Legumes, such as beans, lentils, and peas, are the richest sources of molybdenum. Grain products and nuts are considered good sources, while animal products, fruit, and many vegetables are generally low in molybdenum (2). Because the molybdenum content of plants depends on the soil molybdenum content and other environmental conditions, the molybdenum content of foods can vary considerably (51, 57).

Supplements

Molybdenum in single-nutrient and multiple nutrient supplements is of various forms, including sodium molybdate, ammonium molybdate, molybdenum citrate, molybdenum chloride, and molybdenum glycinate, among others (58).

Parenteral nutrition

Molybdenum may be present in solutions of parenteral nutrition either included as a trace element or as an incidental contaminant (59, 60).

Safety

Toxicity

The toxicity of molybdenum compounds appears to be relatively low in humans. Increased serum concentrations of uric acid and ceruloplasmin (an iron-oxidizing enzyme) have been reported in occupationally exposed workers in a molybdenite roasting plant (61). Gout-like symptoms have also been reported in an Armenian population consuming 10 to 15 milligrams (mg) of molybdenum from food daily (62). In other studies, blood and urinary uric acid concentrations were not elevated by molybdenum intakes up to 1.5 mg/day (2). There has been only one report of acute toxicity related to molybdenum from a dietary supplement: an adult male reportedly consumed a total of 13.5 mg of molybdenum over a period of 18 days (300 to 800 μg/day) and developed acute psychosis with hallucinations, seizures, and other neurologic symptoms (63). However, a controlled study in four, healthy young men found that molybdenum intakes, ranging from 22 μg/day to 1,490 μg/day (almost 1.5 mg/day), elicited no serious adverse effects when molybdenum was given for 24 days (47).

The Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) found little evidence that molybdenum excess was associated with adverse health outcomes in generally healthy people. To determine the tolerable upper intake level (UL), the FNB selected adverse reproductive effects in rats as the most sensitive index of toxicity and applied a large uncertainty factor because animal data were used (2). The UL for molybdenum is listed by age group in **Table 2**.

Table 2. Tolerable Upper Intake Level (UL) for Molybdenum

Age Group	UL (μg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	300
Children 4-8 years	600
Children 9-13 years	1,100 (1.1 mg/day)
Adolescents 14-18 years	1,700 (1.7 mg/day)
Adults 19 years and older	2,000 (2.0 mg/day)
*Source of intake should be from food and formula only.	

Drug interactions

High doses of molybdenum have been found to inhibit the metabolism of acetaminophen in rats (64); however, it is not known whether this occurs at clinically relevant doses in humans.

Linus Pauling Institute Recommendation

The RDA for molybdenum (45 μg/day for adults) is sufficient to prevent deficiency. Although the intake of molybdenum most likely to promote optimum health is not known, there is presently no evidence that intakes higher than the RDA are beneficial. Most people in the US consume more than sufficient molybdenum in their diets, making supplementation unnecessary. Following the Linus Pauling Institute's general recommendation to take a multivitamin/mineral supplement that contains 100% of the daily values (DV) for most nutrients is likely to provide 45 μg/day of molybdenum.

Older adults (>50 years)

Because aging has not been associated with significant changes in the requirement for molybdenum (2), our recommendation for older adults is the same as that for adults 50 years and younger.

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# Phosphorus

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Español

Summary

- Phosphorus is an essential structural component of cell membranes and nucleic acids but is also involved in several biological processes, including bone mineralization, energy production, cell signaling through phosphorylation reactions, and regulation of acid-base homeostasis. *(More information)*
- Dietary phosphorus deficiency is uncommon and often only observed in cases of near-total starvation or in rare inherited disorders involving renal phosphorus wasting. Symptoms include loss of appetite, muscle weakness, bone fragility, numbness in the extremities, and rickets in children. *(More information)*
- The Recommended Dietary Allowance (RDA), 700 mg/day of phosphorus for healthy adults, is meant to sustain serum phosphorus concentrations within the physiologic range of 2.5 to 4.5 mg/dL. *(More information)*
- Phosphorus is found in most food sources and is a component of many commonly used food additives. The bioavailability of phosphorus from food is usually very high with the exception of phytate phosphorus in plant sources, such as grains, legumes, and seeds, which is poorly digested. *(More information)*
- Estimates of dietary phosphorus intakes in the US population are likely to be inaccurate because the amounts of phosphorus-based food additives used in processed foods are not always included in the nutrient content database used to compute nutrient intakes. *(More information)*
- High serum phosphorus concentrations have been associated with increased rates of cardiovascular disease and mortality in subjects with or without kidney disease. Abnormal deposition of calcium phosphate in soft tissues may predispose individuals to vascular dysfunction and cardiovascular disease. *(More information)*
- Hyperphosphatemia, which is common in individuals with impaired kidney function, characterizes a condition in which there is an abnormally high accumulation of phosphorus in blood, because the kidneys are not able to effectively excrete it. *(More information)*
- The tolerable upper intake level (UL) for phosphorus is 4,000 mg/day for generally healthy adults. Yet, daily phosphorus intakes in excess of the RDA have been linked to an increased risk of all-cause mortality in healthy individuals. *(More information)*
- Observational studies suggest that a low calcium-to-phosphorus intake ratio may be detrimental to bone health, especially in women at increased risk for osteoporosis. *(More information)*

Phosphorus is an essential mineral that is required by every cell in the body for normal function (1). Bound to oxygen in all biological systems, phosphorus is found as phosphate (PO_4^{3-}) in the body. Approximately 85% of the body's phosphorus is found in bones and teeth (2).

Function

Phosphorus is a major structural component of bone in the form of a calcium phosphate salt called hydroxyapatite. Phospholipids (e.g., phosphatidylcholine) are major structural components of cell membranes. All energy production and storage are dependent on phosphorylated compounds, such as adenosine triphosphate (ATP) and creatine phosphate. Nucleic acids (DNA and RNA), which are responsible for the storage and transmission of genetic information, are long chains of phosphate-containing molecules. A number of enzymes, hormones, and cell-signaling molecules depend on phosphorylation for their activation. Phosphorus also helps maintain normal acid-base balance (pH) by acting as one of the body's most important buffers. Additionally, the phosphorus-containing molecule 2,3-diphosphoglycerate (2,3-DPG) binds to hemoglobin in red blood cells and regulates oxygen delivery to the tissues of the body (1).

Regulation

Parathyroid hormone-vitamin D and FGF-23-endocrine axis

Dietary phosphorus is readily absorbed in the small intestine, and in healthy individuals, excess phosphorus is excreted by the kidneys under the regulatory action of the endocrine hormones: parathyroid hormone (PTH), vitamin D, and fibroblast growth factor-23 (FGF-23). The acute regulation of blood calcium and phosphorus concentrations is controlled through the actions of PTH and the active form of vitamin D. A slight drop in blood calcium levels (e.g., in the case of inadequate calcium intake) is sensed by the parathyroid glands, resulting in their increased secretion of PTH, which rapidly decreases urinary excretion of calcium but increases urinary excretion of phosphorus and stimulates bone resorption. This results in the release of bone mineral (calcium and phosphate) — actions that restore serum calcium concentrations. Although the action is not immediate, PTH also stimulates conversion of vitamin D to its active form (1,25-dihydroxyvitamin D; calcitriol) in the kidneys. Increased circulating 1,25-dihydroxyvitamin D in turn stimulates increased intestinal absorption of both calcium and phosphorus. A third hormone, FGF-23, plays a central role in phosphorus homeostasis. FGF-23 is secreted by bone-forming cells (osteoblasts/osteocytes) in response to increases in phosphorus intake. In a negative feedback loop, FGF-23 inhibits the production and stimulates the degradation of 1,25-dihydroxyvitamin D, as well as promotes an increase in urinary phosphorus excretion independently of PTH and 1,25-dihydroxyvitamin D (3).

Deficiency

Inadequate phosphorus intake rarely results in abnormally low serum phosphorus levels (hypophosphatemia) because renal reabsorption of phosphorus increases to compensate for decreased intake. The effects of moderate to severe hypophosphatemia may include loss of appetite, anemia, muscle weakness, bone pain, rickets (in children), osteomalacia (in adults), increased susceptibility to infection, numbness and tingling of the extremities, difficulty walking, and respiratory failure. Severe hypophosphatemia may occasionally be life threatening. Since phosphorus is so widespread in food, dietary phosphorus deficiency is usually seen only in cases of near-total starvation. Other individuals at risk of hypophosphatemia include alcoholics, diabetics recovering from an episode of diabetic ketoacidosis, patients with respiratory alkalosis, and starving or anorexic patients on refeeding regimens that are high in calories but too low in phosphorus (reviewed in 4). Hypophosphatemia caused by inherited disorders of phosphorus homeostasis (phosphorus wasting disorders) has been linked to elevated urinary excretion or impaired renal reabsorption of phosphorus in affected subjects (reviewed in 5).

The Recommended Dietary Allowance (RDA)

The Recommended Dietary Allowance (RDA) for phosphorus is based on the maintenance of normal serum phosphorus levels in adults (2.5-4.5 milligrams/deciliter [mg/dL]) and is believed to represent adequate phosphorus intakes to meet cellular and bone formation needs (6; **Table 1**). The RDA, which is the average daily intake that meets the requirements of 97.5% of healthy individuals in a specific life stage and gender group, is based on the Estimated Average Requirement (EAR; 580 mg/day of phosphorus for adults) — the nutrient intake that meets the requirements of 50% of healthy individuals in a particular life stage and gender group.

Table 1. Recommended Dietary Allowance (RDA) for Phosphorus

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	100 (AI)	100 (AI)
Infants	7-12 months	275 (AI)	275 (AI)
Children	1-3 years	460	460
Children	4-8 years	500	500
Children	9-13 years	1,250	1,250
Adolescents	14-18 years	1,250	1,250
Adults	19 years and older	700	700
Pregnancy	18 years and younger	-	1,250
Pregnancy	19 years and older	-	700
Breast-feeding	18 years and younger	-	1,250
Breast-feeding	19 years and older	-	700

Sources

Food sources

Phosphorus is found in most food because it is a critical constituent of all living organisms. Dairy foods, cereal products, meat, and fish are particularly rich sources of phosphorus (7). Phosphorus is also a component of many food additives that are used in food processing and is present in cola soft drinks as phosphoric acid (8). In the nationally representative NHANES survey, phosphorus intakes were well above the EAR and RDA, with average daily intakes of 1,602 mg in men and 1,128 mg in women (8). Dietary phosphorus derived from food additives is not always included in food nutrient composition databases, so the total amount of phosphorus consumed by the average person in the US can be underestimated by more than 20% (9). Segments of the US population who consume more highly processed foods and whose phosphorus intakes approach the tolerable upper intake level of 4,000 mg/day are thought by some to be at high risk of developing adverse health outcomes (see Safety) (7, 9).

Bioavailability

The phosphorus in plant seeds (beans, peas, cereals, and nuts) is present in a storage form of phosphate called phytic acid or phytate. Only about 50% of the phosphorus from phytate is available to humans because we lack enzymes (phytases) that liberate phosphorus from phytate (10). Yeasts possess phytases, so whole grains incorporated into leavened breads have more bioavailable phosphorus than whole grains incorporated into breakfast cereals or flat breads (6). Because reducing dietary phosphorus absorption may benefit individuals with impaired kidney function who are at risk of hyperphosphatemia (serum phosphorus at or above the high-normal range), protein sources of phosphorus in grain-based vegetarian diets may be preferred over meat-based diets (11). **Table 2** lists a number of phosphorus-rich foods, along with their phosphorus content in milligrams (mg). For more information on the nutrient content of food, search USDA's FoodData Central.

Table 2. Some Food Sources of Phosphorus

Food	Serving	Phosphorus (mg)
Salmon (chinook, cooked)	3 ounces*	315
Yogurt (plain, nonfat)	8 ounces	306
Milk (skim)	8 ounces	247
Halibut (Atlantic or Pacific, cooked)	3 ounces	244
Turkey (light meat, cooked)	3 ounces	217
Chicken (light meat, cooked)	3 ounces	135-196
Beef (chuck eye steak, cooked)	3 ounces	179
Lentils# (cooked)	½ cup	178
Almonds#	1 ounce (23 nuts)	136
Cheese, mozzarella (part skim)	1 ounce	131
Peanuts#	1 ounce	108
Egg (hard-boiled)	1 large	86
Bread, whole-wheat	1 slice	68
Carbonated cola drink	12 ounces	41
Bread, enriched white	1 slice	25
*A three-ounce serving of meat or fish is about the size of a deck of cards. #Phosphorus from nuts, seeds, and grains is about 50% less bioavailable than phosphorus from other sources (12).		

Supplements

Phosphorus content of multivitamin/mineral (MVM) supplements varies; a US national survey found that MVM supplements contributed an average of 108 mg to daily phosphorus intake (10). Sodium phosphate and potassium phosphate salts are used for the treatment of hypophosphatemia that occurs in hereditary disorders of phosphate wasting, and their use requires medical supervision. Calcium phosphate salts are sometimes used as calcium supplements (13). Commonly used over-the-counter and prescription drugs also contribute to phosphorus intakes at levels yet to be defined (10).

Safety

Toxicity

Several disorders characterized by serum phosphorus levels above normal (hyperphosphatemia) have been described, including those resulting from increased intestinal absorption of phosphate salts taken by mouth or by colonic absorption of the phosphate salts in enemas (1). Yet, the disruption of phosphorus homeostasis is most often associated with excretion failure in patients with chronic kidney disease (CKD) or end-stage renal disease (advanced CKD). When kidney function is only 20% of normal, even phosphorus intakes within the recommended range may lead to hyperphosphatemia. Hyperphosphatemia may also affect individuals with inappropriately low parathyroid hormone (PTH) levels (hypoparathyroidism) as they lack PTH stimulation of renal phosphate excretion and fail to stimulate synthesis of 1,25-dihydroxyvitamin D (the active form of vitamin D). These individuals cannot excrete excess phosphorus in the absence of both hormones (14). Elevated serum phosphorus concentrations have been associated with accelerated disease progression in individuals with impaired kidney function and have been linked to increased risk of adverse health outcomes in the general population (9, 15).

High serum phosphorus concentrations in the general population

High serum phosphorus within the normal range (2.5-4.5 mg/dL) has recently been associated with increased incidence of cardiovascular disease (CVD) in individuals with normal kidney function. Two studies conducted in the general population and in individuals with prior CVD have linked high-normal serum phosphorus concentrations (≥3.5 mg/dL) to a greater cardiovascular risk (16, 17). Additional observational studies found that serum phosphorus concentrations equal to or above 4 mg/dL were associated with a doubling of the risk of developing incident CKD and end-stage renal disease in individuals free of renal disease at study inception (18). In a prospective cohort study, which followed 4,005 healthy young adults for more than 15 years, higher serum phosphorus within the normal range was also associated with left ventricular hypertrophy, a condition often linked to adverse cardiovascular outcomes (19). In another study of 3,088 middle-aged healthy participants followed for over 17 years, serum phosphorus concentrations in the top quartile of the normal range were associated with a two-fold higher risk of heart failure compared to the lowest quartile (≥3.5 mg/dL vs. <2.9 mg/dL) (16). It is thought that vascular calcification, which may explain the relationship between high phosphorus and cardiovascular disease risk in CKD patients (see Hyperphosphatemia in subjects with kidney disease), contributes to this association in individuals with normal kidney function, even when their serum phosphorus is within the normal range and their intakes are below the tolerable upper intake level (UL) (20, 21).

Phosphorus homeostasis is tightly regulated by the PTH/vitamin D/FGF-23 axis in individuals with normal kidney function (see Regulation). Increased secretion of PTH and FGF-23 helps maintain phosphorus serum concentrations in the normal range (2.5-4.5 mg/dL) even in the setting of high phosphorus intake (9). This contributes to serum phosphorus being only weakly correlated to phosphorus consumption (22). Of note, sustained increases in FGF-23 and PTH are commonly observed during CKD in order to maintain normal serum phosphorus concentrations despite a reduction in urinary phosphorus excretion (23). Elevated FGF-23, rather than serum phosphorus, appears to be an early marker of disordered phosphorus homeostasis and a predictor of adverse health outcomes in patients with early-stage CKD (23, 24). Thus, it is reasonable to assume that measuring serum phosphorus in people with normal renal function cannot adequately reflect early disturbances in phosphorus metabolism due to high phosphorus consumption.

Hyperphosphatemia in subjects with kidney disease

Observational studies have reported high rates of mortality and cardiovascular events in association with high blood phosphorus levels in subjects with CKD. A meta-analysis of 13 prospective cohort studies, conducted in over 90,000 CKD patients, found an 18% increase in all-cause mortality per 1 mg/dL increase in serum phosphorus concentration above 3.5 mg/dL. A 10% increased risk in cardiovascular disease (CVD)-related death was also calculated for each 1 mg/dL higher concentration in the meta-analysis of three studies (25).

Although no causality has been established between vitamin D deficiency and CVD risk, it has been suggested that failure to produce 1,25-dihydroxyvitamin D in hyperphosphatemic individuals may modify the risk of developing cardiovascular and renal disease, as well as worsen kidney insufficiency in CKD patients (26). Another plausible mechanism for hyperphosphatemia-induced cardiovascular dysfunction is the deposition of calcium phosphate in non-skeletal tissues, especially the vasculature (27). Indeed, high phosphorus concentrations may stimulate the expression of bone specific markers in blood vessel-forming cells, resulting in a shift in their functions; this process, called osteochondrogenic differentiation, transforms vascular smooth muscle cells (VSMCs) into bone-like cells. The culture of human aortic VSMCs in hyperphosphatemic conditions was found to result in the mineralization of the extracellular media, mimicking *in vivo* vascular calcification (28). Vascular calcification has been associated with at least a three-fold increase in risk for cardiovascular events and mortality; the risk for cardiovascular events is twice as high (i.e., six-fold increased risk) in individuals with kidney insufficiency (29).

In CKD patients, disorders in bone remodeling may result in excess release of phosphorus and calcium into the blood, which exacerbates hyperphosphatemia and vascular calcification and accelerates the decline of kidney function. Currently, dietary phosphorus restriction is recommended to normalize serum concentrations in CKD patients, although the impact on CVD and mortality risks is not known.

The Tolerable Upper Intake Level (UL)

To avoid the adverse effects of hyperphosphatemia, the US Food and Nutrition Board set a tolerable upper intake level (UL) for oral phosphorus in generally healthy individuals (6; **Table 3**). The lower UL for individuals over 70 years of age, compared to younger age groups, reflects the increased likelihood of impaired kidney function in elderly individuals. The UL does not apply to individuals with significantly impaired kidney function or other health conditions known to increase the risk of hyperphosphatemia.

Table 3. Tolerable Upper Intake Level (UL) for Phosphorus

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	3,000 (3.0 g)
Children 4-8 years	3,000 (3.0 g)
Children 9-13 years	4,000 (4.0 g)
Adolescents 14-18 years	4,000 (4.0 g)
Adults 19-70 years	4,000 (4.0 g)
Adults 71 years and older	3,000 (3.0 g)
Pregnancy	3,500 (3.5 g)
Breast-feeding	4,000 (4.0 g)
*Source of intake should be from food and formula only.	

Adverse health outcomes have been associated with normal serum phosphorus concentrations, suggesting that in individuals with adequate kidney function, the measurement of tightly controlled serum phosphorus levels may misrepresent the detrimental effect of high dietary phosphorus intake (see High serum phosphorus concentrations in the general population). While phosphorus intakes below the UL of 4,000 mg/day should not result in hyperphosphatemia or cardiovascular risk in healthy adults ages 19-70 years, a recent study found that daily phosphorus intakes more than twice the RDA (i.e., >1,400 mg/day) were significantly associated with an increased risk of all-cause mortality (30).

Is high phosphorus intake detrimental to bone health?

Some investigators are concerned about the increasing amounts of phosphates in the diet, which they largely attribute to phosphoric acid in some soft drinks and the increasing use of phosphate additives in processed foods (31, 32). High serum phosphorus has been shown to impair synthesis of the active form of vitamin D (1,25-dihydroxyvitamin D) in the kidneys, reduce blood calcium, and lead to increased PTH release by the parathyroid glands (8). PTH stimulation then results in decreased urinary calcium excretion and increased bone resorption; both contribute to serum calcium concentrations returning to normal (8). If sustained, elevated PTH levels could have an adverse effect on bone mineral content, but this effect appears to be observed with diets that are high in phosphorus and low in calcium, underscoring the importance of a balanced dietary calcium-to-phosphorus ratio. In a small cross-sectional study, which enrolled 147 premenopausal women with adequate calcium intakes, participants with lower calcium-to-phosphorus (Ca:P) intakes (ratios ≤0.5) had significantly higher serum PTH levels and urinary calcium excretion than those with higher Ca:P ratios (ratios >0.5) (33). A controlled trial in 10 young women found no adverse effects of a phosphorus-rich diet (3,000 mg/day) on bone-related hormones and biochemical markers of bone resorption when dietary calcium intakes were maintained at almost 2,000 mg/day (Ca:P = 0.66), again demonstrating the importance of the balance between dietary calcium and phosphorus (34).

A cross-sectional study conducted in 2,344 Brazilian men and women (median age, 58 years) showed an association between higher phosphorus intakes and increased risk of fracture. Yet, intakes of other minerals and vitamins relevant to bone health, such as calcium, magnesium, and vitamin D, were below the RDA in this population, whereas phosphorus intakes were close to the RDA (35). While it appears that hormonal and calcium disorders might be prevented by an adequate calcium-to-phosphorus intake ratio, there is no convincing evidence that the dietary phosphorus levels experienced in the US adversely affect bone mineral density. Nevertheless, the substitution of phosphate-containing soft drinks and snack foods for milk and other calcium-rich food may represent a serious risk to bone health (see the article on Calcium) (36).

Drug interactions

Aluminum-containing antacids reduce the absorption of dietary phosphorus by forming aluminum phosphate, which is unabsorbable. When consumed in high doses, aluminum-containing antacids can produce abnormally low blood phosphorus levels (hypophosphatemia), as well as aggravate phosphorus deficiency due to other causes (37). The reduction of stomach acidity by proton-pump inhibitors may also limit the efficacy of phosphate-binder therapy in patients with kidney failure (38). Excessively high doses of 1,25-dihydroxyvitamin D, the active form of vitamin D, or its analogs, may result in hyperphosphatemia (6).

Potassium supplements or potassium-sparing diuretics taken together with phosphorus supplements may result in high blood levels of potassium (hyperkalemia). Hyperkalemia can be a serious problem, resulting in life-threatening heart rhythm abnormalities (arrhythmias). People taking such a combination must inform their health care provider and have their serum potassium levels checked regularly (37).

Additionally, prevention of bone demineralization by hormone replacement therapy in postmenopausal women is associated with higher urinary phosphorus excretion and lower serum phosphorus levels in treated compared to untreated women (39, 40).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the RDA for phosphorus (700 mg/day for adults). Although some multivitamin/mineral supplements contain more than 15% of the current RDA for phosphorus, a varied diet should easily provide adequate phosphorus for most people.

Older adults (>50 years)

At present, there is no evidence that phosphorus requirements of older adults differ from that of younger adults, and a varied diet should easily provide the RDA (700 mg/day) of phosphorus for those over 50 years of age.

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Potassium

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Summary

- Potassium is considered to be a "nutrient of public health concern" according to the 2015-2020 Dietary Guidelines for Americans since its underconsumption in the US population is associated with adverse health effects (hypertension and cardiovascular disease). *(More information)*
- Normal body function depends on tight regulation of potassium concentrations both inside and outside of cells. *(More information)*
- Low potassium concentration in blood (hypokalemia) can result in muscular paralysis or abnormal heart rhythms and can be fatal. Hypokalemia is usually due to excessive loss of potassium as with prolonged vomiting or diarrhea, use of diuretics, or with kidney disease. *(More information)*
- Chronic hypertension damages the heart, blood vessels, and kidneys, thereby increasing the risk of cardiovascular disease. Increasing dietary potassium intake may help lower blood pressure in normotensive and hypertensive individuals. *(More information)*
- Results from observational studies reported higher dietary potassium intakes to be associated with lower risks of stroke and kidney stone formation. Evidence of a role for potassium intakes in promoting bone health remains weak. *(More information)*
- The adequate intake (AI) for potassium is 2,600 mg/day for women and 3,400 mg/day for men. The AI for each age/life stage group was set based on the level of intake reported in apparently healthy populations. *(More information)*
- Good dietary sources of potassium include fruit and vegetables, some nuts and seeds, and dairy products. *(More information)*
- Safety concerns with consuming potassium are limited in healthy people because the kidneys adjust urinary potassium excretion to potassium intake. Concomitant use of potassium supplements with certain drugs can increase the risk of potassium toxicity. *(More information)*

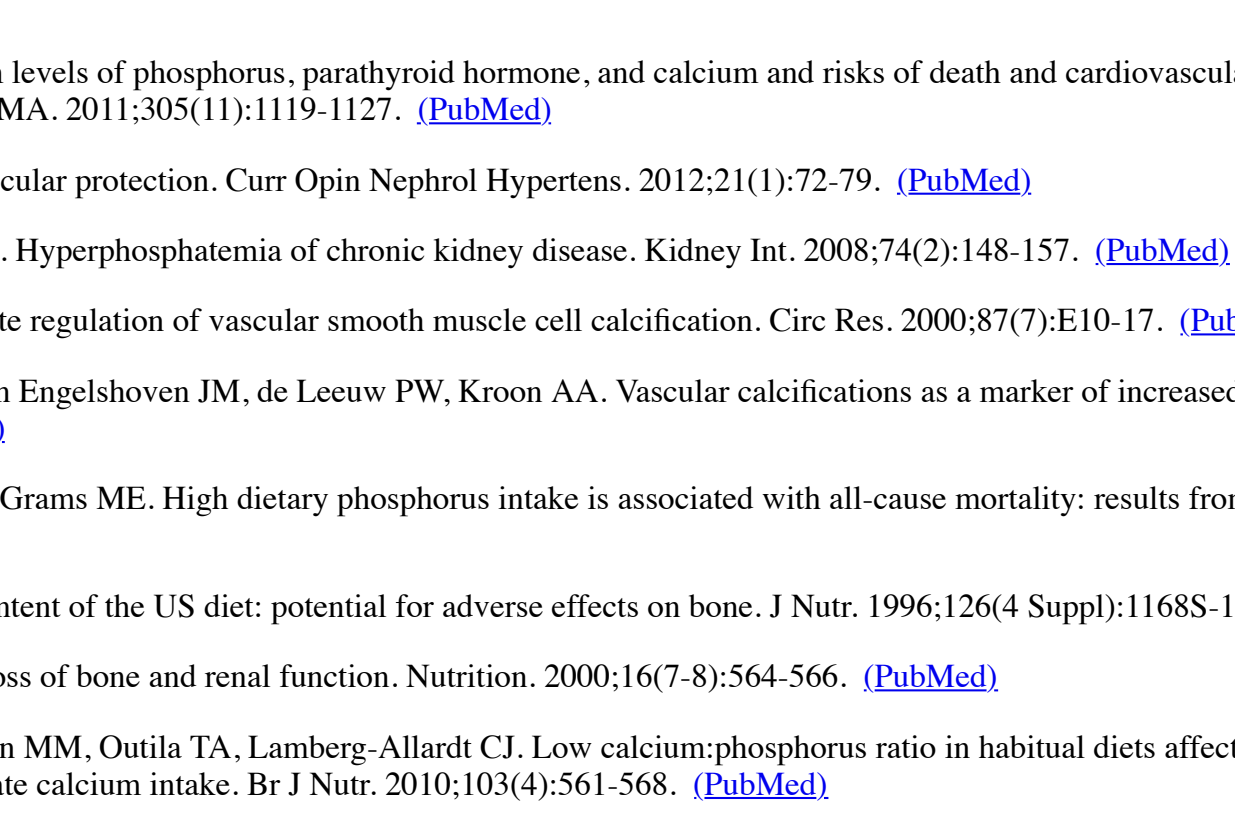
Potassium is an essential dietary mineral and electrolyte. The term electrolyte refers to a substance that dissociates into ions (charged particles) in solution, making it capable of conducting electricity. Normal body function depends on tight regulation of potassium concentrations both inside and outside of cells (1).

Function

Maintenance of membrane potential

Potassium (K^+) is the principal positively charged ion (cation) in the fluid inside of cells, while sodium (Na^+) is the principal cation in the extracellular fluid. Potassium concentrations are about 30 times higher inside than outside cells, while sodium concentrations are more than 10 times lower inside than outside cells. The concentration differences between potassium and sodium across cell membranes create an electrochemical gradient known as the membrane potential. A cell's membrane potential is maintained by ion pumps in the cell membrane, especially the Na^+/K^+-ATPase pumps. These pumps use ATP (energy) to pump sodium out of the cell in exchange for potassium (**Figure 1**). Their activity has been estimated to account for 20%-40% of the resting energy expenditure in a typical adult. The large proportion of energy dedicated to maintaining sodium/potassium concentration gradients emphasizes the importance of this function in sustaining life. Tight control of cell membrane potential is critical for nerve impulse transmission, muscle contraction, and heart function (2-4).

Figure 1. A Simplified Model of the Na^+/K^+ATPase Pump



Differences in concentrations of potassium (K^+) and sodium (Na^+) ions across cell membranes create an electrochemical gradient known as the membrane potential. The concentration of K^+ is typically 20-30 times higher inside compared to outside the cells whereas Na^+ is in higher concentration in the extracellular compared to the intracellular compartment. Therefore, K^+ diffuses easily out of the cells whereas Na^+ diffuses easily into the cells. The Na^+/K^+ ATPase pump is thus required to maintain the membrane potential by pumping Na^+ out of the cells and K^+ into the cells. In the presence of magnesium (Mg^{2+}), adenosine triphosphate (ATP) provides the energy to translocate 3 Na^+ ions and 2 K^+ ions across the plasma membrane against their concentration gradients. The binding of ATP and magnesium (Mg^{2+}) allows the enzyme to adopt a conformation that opens toward the cytoplasm for the binding and the translocation of Na^+ ions; In turn, the binding of K^+ ions induces the release of phosphate and Mg^{2+} and the translocation of K^+ ions to the cytoplasm.

[Figure 1 - Click to Enlarge]

Cofactor for enzymes

A limited number of enzymes require the presence of potassium for their activity. The activation of Na^+/K^+-ATPase requires the presence of sodium and potassium. The presence of potassium is also required for the activity of pyruvate kinase, an important enzyme in carbohydrate metabolism (5).

Deficiency

An abnormally low plasma potassium concentration is referred to as hypokalemia. Hypokalemia is most commonly a result of excessive loss of potassium, e.g., from prolonged vomiting or diarrhea, use of some diuretics and other medications (see Drug interactions), some forms of kidney disease, or metabolic disturbances. The symptoms of hypokalemia are related to alterations in membrane potential and cellular metabolism (1). They include fatigue, muscle weakness and cramps, and intestinal paralysis, which may lead to bloating, constipation, and abdominal pain. Chronic hypokalemia is associated with hypertension and kidney stone formation (see Disease Prevention and Disease Treatment). Severe hypokalemia may result in muscular paralysis or abnormal heart rhythms (cardiac arrhythmias) that can be fatal (1, 6).

Conditions that increase the risk of hypokalemia (see also Drug interactions; 1):

- The use of potassium-wasting diuretics (e.g., thiazide diuretics or furosemide)
- Prolonged vomiting or diarrhea
- Overuse or abuse of laxatives
- Anorexia nervosa or bulimia
- Excessive sweating
- Nephropathies
- Polyuria
- Abnormally high production of aldosterone (hyperaldosteronism)
- Magnesium depletion
- Recovery from prolonged undernutrition

Low dietary potassium intake alone does not generally result in hypokalemia. However, insufficient dietary potassium in patients at risk of hypokalemia can precipitate hypokalemia (1).

In rare cases, habitual consumption of large amounts of black licorice has resulted in hypokalemia (7, 8). Licorice contains a compound (i.e., glycyrrhizic acid) with similar physiologic effects to those of aldosterone, a hormone that increases urinary excretion of potassium.

The Adequate Intake (AI)

The Dietary Reference Intakes (DRIs) for potassium have been recently revised by the Food and Nutrition Board (FNB) of the National Academy of Medicine. The FNB did not find sufficient evidence to determine an Estimated Average Requirement (EAR) and derive a Recommended Dietary Allowance (RDA); instead, they established an adequate intake (AI) based on median intakes in generally healthy people (**Table 1**) (9). The FNB found insufficient evidence from human studies that examined potassium intakes in relation to chronic disease and mortality (reviewed recently by the Agency for Healthcare Research and Quality; 10) to inform the DRIs for potassium (11).

Table 1. Adequate Intake (AI) for Potassium

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	400	400
Infants	7-12 months	860	860
Children	1-3 years	2,000	2,000
Children	4-8 years	2,300	2,300
Children	9-13 years	2,500	2,300
Adolescents	14-18 years	3,000	2,300
Adults	19 years and older	3,400	2,600
Pregnancy	14-18 years	-	2,600
Pregnancy	19-50 years	-	2,900
Breast-feeding	14-18 years	-	2,500
Breast-feeding	19-50 years	-	2,800

Disease Prevention

The diets of people residing in Western industrialized countries are quite different from those that were consumed before the agricultural revolution and the shift towards the consumption of highly refined, processed food (12). Among other differences, the daily intake of sodium chloride (salt) in modern diets is about three times higher than the daily intake of potassium on a molar basis, whereas salt intake in primitive cultures is about seven times lower than potassium intake (13). The relative deficiency of dietary potassium in the modern diet and a higher sodium-to-potassium ratio may contribute to the development of some chronic diseases.

Stroke

Observational studies have consistently reported an increased risk of cardiovascular disease with elevated dietary sodium intakes (14, 15). Several prospective cohort studies have also found an inverse association between potassium intake and risk of stroke. A meta-analysis of nine prospective cohort studies showed that daily potassium intakes ranging between 3,510 mg and 4,680 mg were associated with a 30% reduced risk of stroke (16). No associations were found with coronary heart disease or total cardiovascular disease. In a more recent meta-analysis of 16 studies, the highest versus lowest dietary potassium intake was found to be associated with a 13% lower risk of stroke after multiple adjustments (including for blood pressure) (17). The lowest risk of stroke corresponded to daily potassium intakes around 3,500 mg. Subgroup analyses showed a reduced risk of ischemic stroke, but not hemorrhagic stroke. Finally, in a recent meta-analysis of 16 observational studies, each 1-unit increase in the dietary sodium-to-potassium ratio was found to be associated with a 22% higher risk of stroke (12).

Kidney stones

Abnormally high urinary calcium (hypercalciuria) increases the risk of developing kidney stones. In individuals with a history of developing calcium-containing kidney stones, increased dietary acid load has been significantly associated with increased urinary calcium excretion (18). Increasing dietary potassium (and alkali) intake by increasing fruit and vegetable intake or by taking potassium bicarbonate ($KHCO_3$) supplements has been found to decrease urinary calcium excretion. Conversely, potassium deprivation has been found to increase urinary calcium excretion (19, 20).

Three large US prospective cohort studies — the Health Professionals Follow-up Study and the Nurses' Health Studies I and II — which included 193,676 participants, have examined dietary potassium intake and animal protein-to-potassium ratio (a marker of dietary acid load) in the diet in relation to the risk of developing kidney stones (21). In all three cohorts, dietary potassium intake was derived almost entirely from potassium-rich foods, such as fruit and vegetables. Across the three cohorts, individuals in the highest quintile of potassium intake were found to be 33%-56% less likely to develop symptomatic kidney stones than those in the lowest quintile of intake. Additionally, a pooled analysis of the data from all three cohorts showed that those with the highest versus lowest animal protein-to-potassium ratio were 41% more likely to develop kidney stones (21).

Urinary alkalinization with supplemental potassium citrate is used in stone formers to reduce the risk of recurrent stone formation (reviewed in 22). However, potassium citrate therapy should only be initiated under the supervision of a medical provider.

Osteoporosis

In a 2015 case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, which included 5,319 individuals, dietary intakes of potassium (alone or combined with intakes of magnesium) were found to be inversely associated with heel bone (calcaneus) broadband ultrasound attenuation (BUA) measurements (a predictor of the risk of incidental fracture) and risk of hip fracture in women but not in men (23). More recently, a cross-sectional study in older Korean adults reported higher total hip and femur neck bone mineral density (BMD) in those in the top versus bottom tertile of potassium intakes (24). Although these observational studies suggest a link between potassium intakes and bone health, they cannot establish whether there is a cause-and-effect relationship.

The mechanisms by which potassium might influence bone health are poorly understood. Modern (Western) diets tend to be relatively low in sources of alkali (fruit and vegetables) and high in sources of acid (fish, meat, and cheese) (25). When the quantity of bicarbonate ions is insufficient to maintain normal pH, the body is capable of mobilizing alkaline calcium salts from bone in order to neutralize acids consumed in the diet or generated by metabolism (26). Because fruit and vegetables are rich in both potassium and precursors to bicarbonate ions, increasing their consumption might help reduce the net acid content of the diet and preserve calcium in bones, which might otherwise be mobilized to maintain normal pH (see the article on Fruit and Vegetables).

Alternatively, potassium bicarbonate supplementation might decrease urinary acid and calcium excretion and influence bone turnover — a small trial in postmenopausal women found that potassium bicarbonate supplementation increases biomarkers of bone formation and a decreased biomarkers of bone resorption (27). A two-year randomized, double-blind, controlled trial in 201 older adults without osteoporosis (mean age, 69 years) found evidence of increased lumbar spine, hip, femoral neck, and total-body BMD, as well as trabecular BMD of the radius and tibia, with supplemental potassium citrate (2,340 mg/day) compared to placebo (28). Potassium citrate was also found to increase the serum concentration of N-terminal propeptide of type I procollagen (PINP) — a marker of bone formation — and reduce the urine concentration of N-telopeptide of collagen type I (NTX) — a marker of bone resorption (28). Another three-month, randomized, placebo-controlled trial in 244 adults (≥50 years) examined the effect of oral potassium bicarbonate, at either 39 mg/kg/day or 58.5 mg/kg/day, on markers of bone turnover (29). Both dosage regimens led to reductions in serum PINP concentration and urine NTX concentration, yet evidence of an effect was stronger with the lowest dose (median dose administered, 3,160 mg/day) rather than with the highest dose (median dose administered, 4,760 mg/day). In contrast, a two-year randomized controlled trial found that neither supplementation with potassium citrate (721 mg/day or 2,165 mg/day) nor an increase in fruit and vegetable intake (300 mg/day) had an impact on markers of bone turnover or increased BMD in postmenopausal women (30). A 2015 meta-analysis of intervention studies found that supplemental potassium citrate or potassium bicarbonate could reduce urinary net acid and calcium excretion, but evidence to support an effect on markers of bone turnover and bone density was weak (31). The most recent randomized, double-blind, controlled trial in 40 postmenopausal women with osteopenia found no difference in markers of bone turnover over a six-month period between those supplemented with potassium citrate and those taking a placebo (32). The authors highlighted the possibility that an effect of supplemental potassium might have an impact on bone health in a subset of subjects with low potassium intakes and/or signs of low-grade acidosis. In this study, all participants received daily supplements of calcium carbonate (500 mg/day) and vitamin D (10 μg/day).

Overall, whether consuming potassium-rich fruit and vegetables can influence bone health and help lower the risk of osteoporosis remains uncertain (see also the article on Fruit and Vegetables).

Disease Treatment

Hypertension

Forty-five percent of US adults have hypertension (blood pressure levels ≥130/80 mm Hg) (33). Chronic hypertension damages the heart, blood vessels, and kidneys, thereby increasing the risk of heart disease and stroke, as well as hypertensive kidney disease (34, 35). Modern diets, which are high in sodium and low in potassium, are recognized as largely contributing to the high prevalence of hypertension (see the article on Sodium). Unlike 24-hour dietary recalls, 24-hour urine collections provide accurate estimates of dietary intakes of sodium and potassium (36). An analysis of the 2014 US National Health and Nutrition Examination Survey (NHANES) showed an increase in systolic blood pressure with increasing sodium excretion and increasing sodium-to-potassium ratio in the urine (37). In this study, the highest versus lowest quartile of urinary potassium excretion (mid-values, 3,043 mg/day versus 1,484 mg/day) was associated with a 62% lower risk of hypertension (37).

The Dietary Approaches to Stop Hypertension (DASH) trial provided evidence of the blood pressure-lowering effect of a diet higher in potassium and calcium, modestly higher in protein, and lower in total fat, saturated fat, cholesterol, red meat, sweets, and sugar-containing beverages compared to the typical US diet (38). Indeed, compared to the control diet providing only 3.5 servings/day of fruit and vegetables and 1,700 mg/day of potassium, adherence to the DASH diet that included 8.5 servings/day of fruit and vegetables and 4,100 mg/day of potassium lowered systolic/diastolic blood pressures by an average 11.4/5.5 mm Hg in people with hypertension and 3.5/2.1 mm Hg in those without hypertension (38). A 2014 meta-analysis of 17 randomized controlled trials that examined the effect of the DASH diet compared to a control diet in a total of 2,561 adults found overall reductions in systolic and diastolic blood pressure by 6.7 mm Hg and 3.5 mm Hg, respectively (39). However effective the DASH diet is, the blood pressure-lowering effects can hardly be solely attributed to potassium intakes (40).

A 2015 meta-analysis of 15 randomized controlled trials, including 917 individuals, assessed the effects of increased potassium intake, mostly in the form of potassium chloride (KCl) supplements, on blood pressure (41). Thirteen studies included hypertensive participants who were not taking anti-hypertensive medication and two studies included normotensive or at-risk subjects. Most studies used supplemental potassium doses between 2,340 and 2,535 mg/day (60-65 mmol/L). Increased potassium intake resulted in overall reductions of systolic blood pressure by 4.7 mm Hg and diastolic blood pressure by 3.5 mm Hg. The blood pressure-lowering effect of supplemental potassium was more pronounced when the analysis was restricted to individuals with hypertension: systolic and diastolic blood pressure were found to be reduced by 6.8 mm Hg and 4.6 mm Hg, respectively (41). Two additional meta-analyses published in 2017 also confirmed a blood pressure-lowering effect of supplemental potassium. Findings suggested some evidence of a greater effect when baseline potassium intake was less than 3,510 mg/day (vs. ≥3,510 mg/day [90 mmol]) (42). Meta-analyses have also reported a dose-response relationship between the intake of potassium and the lowering of blood pressure (42, 43).

Supplemental potassium can help lower blood pressure, but potassium supplements should only be used in consultation with a medical provider (see Supplements). Increasing potassium intake to recommended levels (see Adequate Intake) by consuming a diet rich in fruit and vegetables can help lower blood pressure and may have additional benefits to health (see the article on Fruit and Vegetables). Blood pressure is a reliable cardiovascular risk marker (44). Yet, although reducing sodium consumption while increasing potassium intake helps with lowering blood pressure (45), current evidence suggests that dietary advice and support interventions may not be sufficient to deliver long-term cardiovascular benefits in individuals with hypertension (46).

Sources

Food sources

The richest sources of potassium are fruit and vegetables. Nuts, seeds, and dairy products are also good sources of potassium. A dietary survey in the US indicated that the average dietary potassium intake was 2,408 mg/day for adult women and 3,172 mg/day for adult men (47). Because many individuals in the population consume potassium in amounts that are well below the AI and because underconsumption of potassium is linked with adverse health effects, potassium has been recognized as a "nutrient of public health concern" in the 2015-2020 Dietary Guidelines for Americans. In 2016, the US Food and Drug Administration (FDA) required manufacturers to display potassium content of foods on the Nutrition Facts food label (48).

Some relatively good dietary sources of potassium are listed in the **Table 2**, along with their potassium content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central (49).

Table 2. Some Food Sources of Potassium

Food	Serving	Potassium (mg)
Potato, baked, with skin	1 medium	926
Apricots, dried	½ cup	755
Beet greens, cooked, boiled	½ cup	654
Plums, dried (prunes)	½ cup	637
Raisins	½ cup	598
Yogurt, plain, low-fat	8 ounces	531
Lima beans, cooked	½ cup	478
Acorn squash, cooked	½ cup (cubes)	448
Banana	1 medium	422
Spinach, cooked	½ cup	419
Tomato juice	6 fluid ounces	395
Orange juice	6 fluid ounces	372
Artichoke, cooked	1 medium	343
100% Prune juice	6 fluid ounces	322
Molasses	1 tablespoon	293
Tomato	1 medium	292
Pistachios	1 ounce	285
Milk	8 ounces	281
Orange	1 medium	238
Almonds	1 ounce	208
Sunflower seeds	1 ounce	137
Egg, whole, cooked	1 large	81

Supplements

Multivitamin-mineral supplements in the US do not contain more than 99 mg of potassium per serving (50). One milliequivalent (mEq) or one millimole (mmol) corresponds to about 39 mg of potassium. Higher doses of supplemental potassium are generally prescribed to prevent and treat potassium depletion and hypokalemia. The use of more potent potassium supplements in potassium deficiency requires close monitoring of serum potassium concentrations. Potassium is available in different supplemental forms, including potassium chloride, potassium citrate, potassium gluconate, potassium bicarbonate, potassium aspartate, and potassium orotate (50). Because of the potential for serious side effects, one should seek medical advice before deciding to use a potassium supplement (see Safety). The best way to increase one's potassium intake is by increasing the consumption of potassium-rich food and beverages (50).

Finally, many salt substitutes contain potassium chloride, and acesulfame potassium (Ace-K) is an FDA-approved general purpose sweetener.

Safety

Toxicity

Abnormally elevated serum potassium concentrations are referred to as hyperkalemia. Hyperkalemia occurs when potassium intake exceeds the capacity of the kidneys to eliminate it. Acute or chronic kidney failure, the use of potassium-sparing diuretics, and insufficient aldosterone secretion (hypoaldosteronism) may result in the accumulation of potassium due to a decreased urinary potassium excretion. Oral doses of potassium >18 g taken at one time in individuals not accustomed to high intakes may lead to severe hyperkalemia, even in those with normal kidney function (6, 50). Hyperkalemia may also result from a shift of intracellular potassium into the circulation, which may occur with the rupture of red blood cells (hemolysis) or tissue damage (e.g., trauma or severe burns). Symptoms of hyperkalemia may include tingling of the hands and feet, muscular weakness, and temporary paralysis. The most serious complication of hyperkalemia is the development of an abnormal heart rhythm (cardiac arrhythmia), which can lead to cardiac arrest (51). A meta-analysis of randomized controlled studies showed that heart rate in healthy adults was unlikely to be affected by the chronic use of supplemental potassium doses of 2 to 3 g/day (52).

See the section on Drug interactions for a discussion of the medications that increase the risk of hyperkalemia.

Adverse reactions to potassium supplements

Gastrointestinal symptoms are the most common side effects of potassium supplements, including nausea, vomiting, abdominal discomfort, and diarrhea. Intestinal ulceration has been reported after the use of enteric-coated potassium chloride tablets. Taking potassium with meals or taking a microencapsulated form of potassium may reduce gastrointestinal side effects (50). Rashes may occasionally occur. The most serious adverse reaction to potassium supplementation is hyperkalemia, yet is rare in subjects with normal kidney function (see Toxicity). Individuals with abnormal kidney function and those on potassium-sparing medications (see Drug interactions) should be monitored closely to prevent hyperkalemia (50, 53).

Drug interactions

Table 3 lists the classes of medications known to increase the risk of hyperkalemia (elevated serum potassium) in patients who also use potassium supplements (50, 51, 54).

Table 3. Medications Associated with Hyperkalemia

Medication Family	Specific Medications
Angiotensin converting enzyme (ACE) inhibitors	captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), ramipril (Altace)
Angiotensin receptor blockers	Losartan (Cozaar), valsartan (Diovan), irbesartan (Avapro), candesartan (Atacand)
Anticoagulant	Heparin
Anti-hypertensive agents	β-blockers, α-blockers
Anti-infective agents	Trimethoprim-sulfamethoxazole, pentamidine
Cardiac glycoside	Digitalis
Nonsteroidal anti-inflammatory agents (NSAID)	Indomethacin, ibuprofen, ketorolac
Potassium-sparing diuretics	spironolactone (Aldactone), triamterene (Dyrenium), amiloride (Midamor)

Several classes of medications are known to induce hypokalemia (low serum potassium; **Table 4**; 55) . In the absence of treatment, hypokalemia can have serious complications and even be fatal (see Deficiency). Various mechanisms explain how certain medications can lead to potassium depletion. For example, both loop and thiazide diuretics increase the urinary excretion of potassium. Corticoids cause sodium retention that leads to a compensatory increase in urinary potassium excretion. Penicillins formulated as sodium salts also stimulate potassium excretion. Several medications, including aminoglycosides, anti-fungal agents (amphotericin-B, fluconazole), and cisplatin, can damage the renal tubular epithelium and lead to severe potassium loss. Outdated tetracycline antibiotics have been linked to electrolyte disturbances.

Table 4. Medications Associated with Hypokalemia

Medication Family	Specific Medications
Aminoglycosides	amikacin (Amikin), gentamicin (Garamycin), kanamycin (Kantrex), tobramycin (Nebcyn), streptomycin
Antibiotics	*Penicillins*: penicillin G sodium (Pfizerpen), mezlocillin (Mezlin), carbenicillin (Geocillin), ticarcillin (Ticar) *Tetracyclines* (when outdated)
Anti-cancer agent	cisplatin (Platinol-AQ)
Anti-fungal agents	amphotericin B (Abelcet, Amphotec, AmBisome, Amphocin, Fungizone), fluconazole (Diflucan)
β-adrenergic agonists	albuterol (Salbutamol, Ventolin), bitolterol (Tornalate), metaproterenol (Alupent)
Diuretics	*Loop diuretics*: bumetanide (Bumex), ethacrynic acid (Edecrin), furosemide (Lasix), torsemide (Demadex) *Thiazide diuretics*: Acetazolamide, thiazides, chlorthalidone (Hygroton), indapamide (Lozol), metolazone (Zaroxolyn), chlorothiazide (Diuril)
Mineralocorticoids	fludrocortisone (Florinef), hydrocortisone (Cortef), cortisone (Cortone), prednisone (Deltasone) *Substances with mineralocorticoid effects*: licorice, carbenoxolone, gossypol
Other	methylxanthines (e.g., theophylline), sodium polystyrene sulfonate, sodium phosphates, caffeine

Linus Pauling Institute Recommendation

There is substantial evidence suggesting that a diet high in potassium-rich food and beverages may be associated with lower risks of stroke, hypertension, kidney stones, and possibly osteoporosis. However, currently there is insufficient evidence to establish a causal relationship between potassium intakes and the risk of these chronic conditions (10). As a consequence, median potassium intakes observed in apparently healthy people were used to set adequate intakes (AI) by age/life stage in the recent revision of the Dietary Reference Intakes (DRIs) for potassium. The revised AI values are 2.6 g/day for women and 3.4 g/day for men (see The Adequate Intake).

Fruit and vegetables are among the richest sources of dietary potassium, and a large body of evidence supports the association of increased fruit and vegetable intakes with reduced risk of cardiovascular disease (see the article on Fruit and Vegetables). The Linus Pauling Institute recommends the consumption of a diet high in potassium-rich foods (see Sources), especially fruit, vegetables, nuts, and dairy products to ensure adequate potassium intakes.

Older adults (>50 years)

A diet rich in fruit and vegetables that supplies 2.6-3.4 g/day of potassium (see AI) should contribute to maintaining a low risk of chronic disease in generally healthy older adults. This recommendation does not apply to individuals who have been advised to limit potassium consumption by a health care professional (see Safety).

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Selenium

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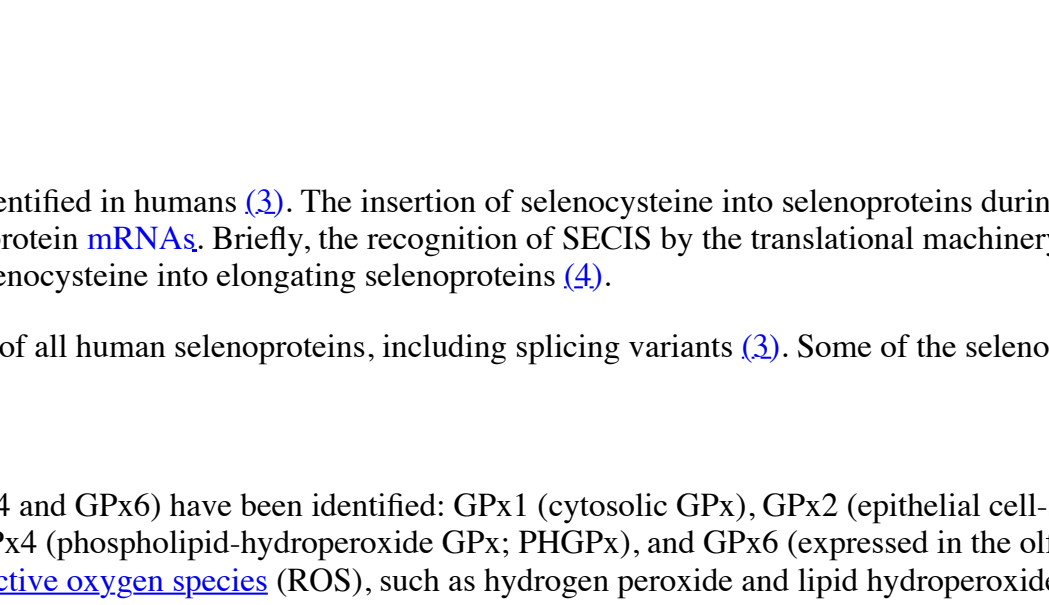
Summary

- Selenium exerts various biological functions mainly as part of the amino acid, selenocysteine, which is found in at least 25 selenocysteine-containing proteins (selenoproteins). *(More information)*
- Five glutathione peroxidases, three thioredoxin reductases, three iodothyronine deiodinases, and one methionine sulfoxide reductase B1 are among the best characterized selenoproteins with known functions. *(More information)*
- Impaired antioxidant protection in selenium-deficient individuals may affect physiological responses to stress. Keshan cardiomyopathy and Kashin-Beck osteoarthropathy are diseases occurring specifically in areas of selenium deficiency in Asia. *(More information)*
- The current recommended dietary allowance (RDA) set by the US Institute of Medicine is 55 μg/day for adolescents and adults of all ages. *(More information)*
- Early observational studies have found either null or inverse associations between selenium exposure and risk of site-specific cancers. However, current evidence from intervention trials in selenium-replete participants does not support a protective effect of selenium supplementation against cancer. *(More information)*
- Preliminary evidence from randomized controlled trials suggests that selenium supplementation may prevent viral load progression and increase immune cell count in HIV-positive patients. *(More information)*
- The levels and chemical forms of selenium in plant-based food vary according to the composition and selenium content of soil in which the plants are grown. Selenium-rich food sources include Brazil nuts, grains, seafood, organ meats, poultry, and dairy products. *(More information)*
- The tolerable upper intake level (UL) for selenium is 400 μg/day for adolescents and adults and includes both selenium obtained from food, which averages about 100 μg/day for adults in the US, and selenium from supplements. *(More information)*
- Because some evidence suggests that high serum selenium concentrations may have adverse effects on glycemic control, individuals with high selenium status and/or those at risk for type 2 diabetes mellitus should avoid taking selenium supplements. *(More information)*

Selenium is a trace element that is essential in small amounts, but like all essential elements, selenium can be toxic at high levels. Unlike plants, most animals — including humans — require selenium for the appropriate functioning of a number of selenium-dependent enzymes known as selenoproteins. During protein synthesis (translation), the amino acid selenocysteine is incorporated into elongating proteins at very specific locations in the amino acid sequence in order to form functional selenoproteins. Although higher plants do not appear to require selenium for survival, they can incorporate it non-specifically into sulfur-containing molecules when the mineral is present in the soil (1). Of note, in animals, the amino acid selenomethionine can be nonspecifically incorporated into proteins in place of methionine (2). However, only selenocysteine-containing proteins are regarded as selenoproteins (**Figure 1**).

Figure 1. Cysteine, Methionine, and Selenium-containing Analogs



Twenty-five human genes code for selenocysteine (Sec)-containing proteins known as selenoproteins. The incorporation of the amino acid Sec into proteins during translation is controlled by a regulatory element (named SECIS) in the 3'-untranslated region of mRNAs coding for selenoproteins. During translation, the recoding of the codon UGA as a signal to insert a Sec (rather than as a "stop codon") into elongating proteins requires the recognition of the SECIS sequence and the presence of a specific Sec-tRNA. Selenomethionine (Se-Met)-containing proteins are not selenoproteins per se. While the incorporation of Sec into selenoproteins is regulated and essential for proper folding and specific selenoprotein functions, the substitution of methionine (Met) with Se-Met is a nonspecific mechanism that does not result in structural and/or functional changes in proteins.

Function

Selenoproteins

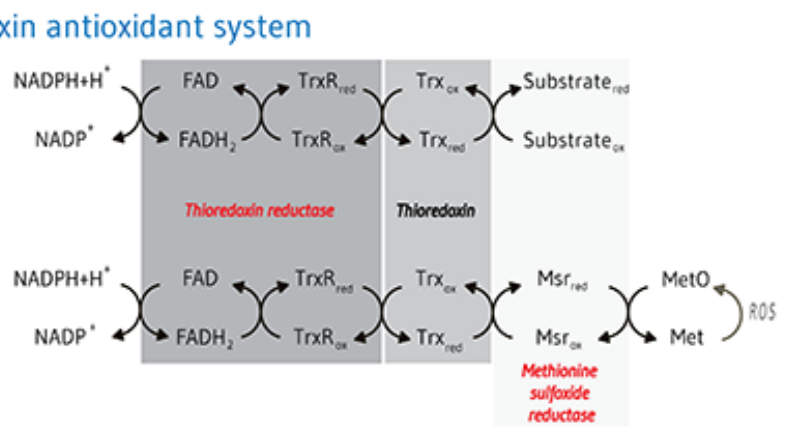
Twenty-five genes coding for selenoproteins have been identified in humans (3). The insertion of selenocysteine into selenoproteins during translation is directed by the presence of a selenocysteine-insertion sequence (SECIS) within selenoprotein mRNAs. Briefly, the recognition of SECIS by the translational machinery results in the recruitment of specific translational factors that decode in-frame UGA codons by inserting selenocysteine into elongating selenoproteins (4).

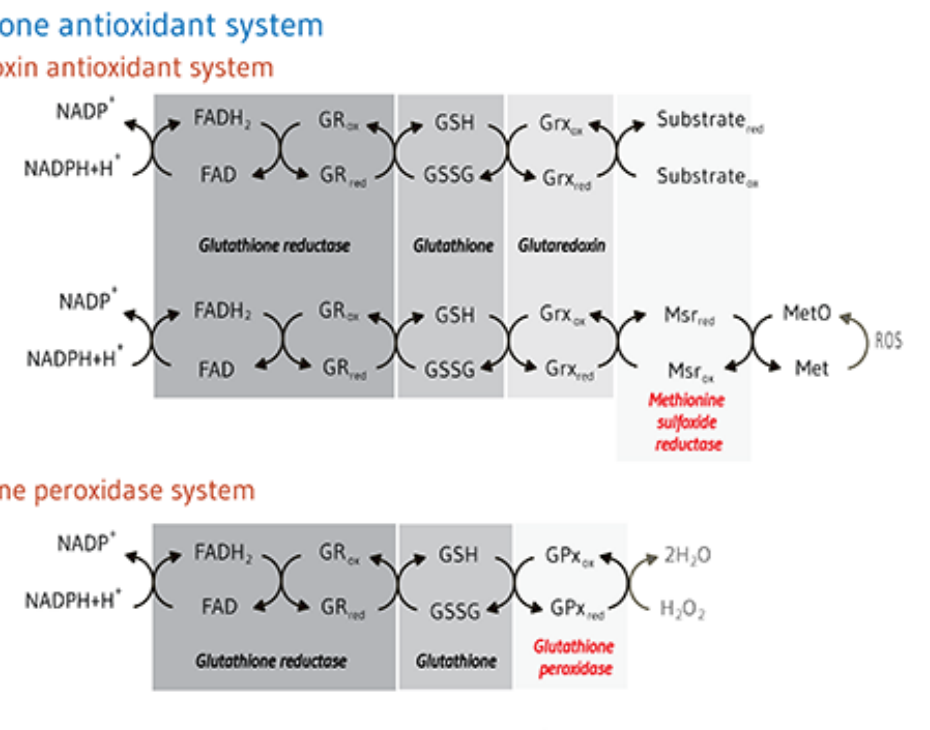
Research is gradually uncovering the metabolic functions of all human selenoproteins, including splicing variants (3). Some of the selenoproteins with an identified function include:

Glutathione peroxidases

Five selenium-containing glutathione peroxidases (GPx1-4 and GPx6) have been identified: GPx1 (cytosolic GPx), GPx2 (epithelial cell-specific GPx expressed in intestinal lining and lungs), GPx3 (highly expressed in thyroid gland and kidneys), GPx4 (phospholipid-hydroperoxide GPx; PHGPx), and GPx6 (expressed in the olfactory epithelium) (4). GPx isoenzymes are all antioxidant enzymes that reduce potentially damaging reactive oxygen species (ROS), such as hydrogen peroxide and lipid hydroperoxides, to harmless products like water and alcohols by coupling their reduction with the oxidation of glutathione (**Figure 2**). Spermatogenesis and male fertility are highly dependent on GPx4 and selenoprotein P (SEPP1; see below). In the testes, GPx4 reduces phospholipid hydroperoxides, hence protecting immature spermatozoa cells against oxidative stress. GPx4 is also a major structural protein of the capsule embedding mature sperm mitochondrial helix involved in sperm motility. SEPP1 is essential for selenium supply to the testes, and animal models lacking the *SEPP1* gene are infertile due to poor selenium tissue bioavailability, defective GPx4 synthesis, and impaired sperm maturation (5).

Figure 2. Selenoproteins in Thiol-based Antioxidant Systems





Selenoproteins (in red) are involved in two major thiol/disulfide-based antioxidant systems: (a) the thioredoxin (Trx) and (b) the glutathione (GSH) antioxidant systems. (a) Substrate reduction by the Trx system results from the transfer of electrons from NADPH to thioredoxin (Trx) via the selenoprotein thioredoxin reductase (TrxR). The family of methionine sulfoxide reductases (Msrs), which includes the selenoenzyme MsrB1 and catalyzes the reduction of methionine sulfoxide (MetO) to methionine (Met), can be readily reduced by both Trx and glutaredoxin (Grx) systems. (b) In the Grx system, electrons are transferred from NADPH to Grx via GSH reductase and GSH. Among the many substrates of the GSH-based redox system is the family of glutathione peroxidases (some of them are selenoenzymes) that can catalyze the conversion of hydrogen peroxide (H_2O_2) to water. *FAD, flavin adenine dinucleotide; GPx, GSH peroxidase; GR, GSH reductase; GSH, glutathione; GSSG, oxidized GSH; Grx, glutaredoxin; H_2O_2, hydrogen peroxide; Met, methionine; MetO, methionine sulfoxide; Msr, methionine sulfoxide reductase; NADP, phosphorylated nicotinamide adenine dinucleotide; ox, oxidized form; red, reduced form; ROS, reactive oxygen species; TrxR, thioredoxin reductase; Trx, thioredoxin.*

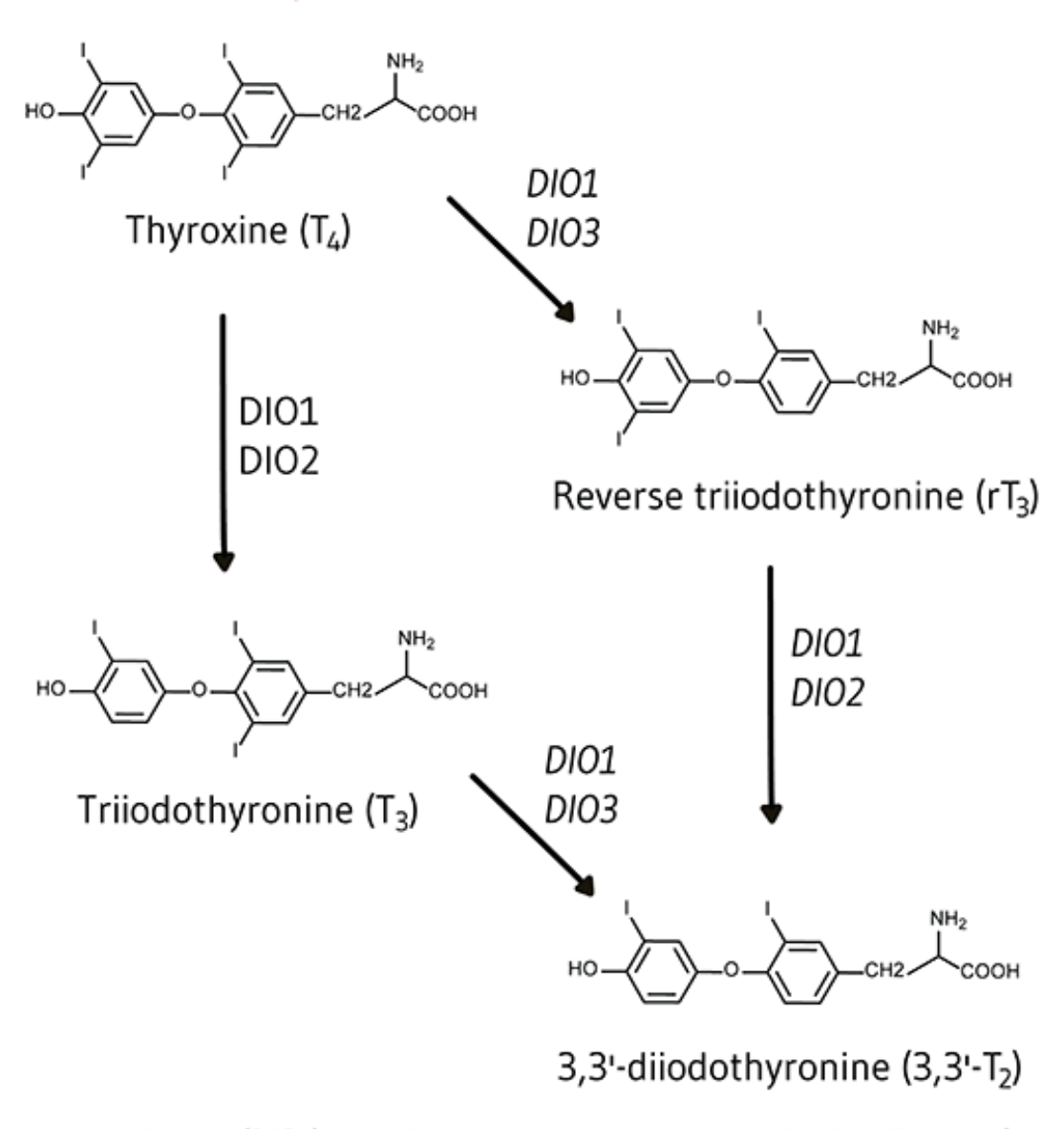
Thioredoxin reductases

In mammals, three selenocysteine-containing thioredoxin reductase (TrxR) isoenzymes have been identified in the thioredoxin system: cytosolic TrxR1, mitochondrial TrxR3, and testes-specific thioredoxin glutathione reductase TGR. TrxRs are homodimeric enzymes, and each monomer contains FAD- and NADPH-binding domains and a selenocysteine-containing catalytic site. TrxRs catalyze the reduction of a wide range of substrates, including thioredoxin and protein disulfide isomerase (PDI) (see **Figure 2** above). TrxRs also serve as electron donors for the regeneration of small antioxidants, possibly recycling ascorbic acid (vitamin C), α-lipoic acid, α-tocopherol (vitamin E), and coenzyme Q_{10} from their oxidized forms (6). The maintenance of thioredoxin in a reduced form by TrxRs is important for regulating cell growth and survival. The protein thioredoxin, together with TrxR1 (or TrxR3), NADPH, and FAD, constitute the thioredoxin antioxidant system involved in the reduction of antioxidant enzymes (e.g., peroxiredoxins, methionine sulfoxide reductases, and ribonucleotide reductase) and of many oxidation/reduction (redox)-sensitive signaling proteins (7). TrxR1 is one of the most investigated selenoproteins and regarded as one of the major antioxidant enzymes and redox regulators in mammalian cells.

Iodothyronine deiodinases (thyroid hormone deiodinases)

The thyroid gland releases very small amounts of biologically active thyroid hormone (triiodothyronine or T_3) and larger amounts of an inactive form of thyroid hormone (T_3 precursor: thyroxine or T_4) into the circulation. Most of the biologically active T_3 in the circulation and inside cells is generated by the removal of one iodine atom from T_4 in a reaction catalyzed by selenium-dependent iodothyronine deiodinase enzymes. Two different selenium-dependent iodothyronine deiodinases (DIOs type 1 and 2) can deiodinate T_4, thus increasing circulating T_3, while a third iodothyronine deiodinase (DIO type 3) can convert both T_3 and T_4 to inactive metabolites (**Figure 3**) (8). Of note, inactivation of the genes encoding DIOs in rodent models has revealed a role for DIO type 1 in iodine homeostasis and the importance of DIOs type 2 and 3 in the maturation of auditory and visual systems during fetal development (8). Thus the importance of selenium in normal development, growth, and metabolism is not limited to its role in the regulation of thyroid gland function.

Figure 3. Deiodination of Thyroid Hormones



Iodothyronine deiodinases (DIOs) are selenoenzymes that catalyze the deiodination (removal of iodine) from iodothyronines. Specifically, DIO1 and DIO2 catalyze the deiodination of thyroxine (T_4) that generates the biologically active triiodothyronine (T_3). DIO3 inactivates T_3 and T_4 by removing iodine atoms from the inner ring.

Selenoprotein P

Selenoprotein P (SEPP1) is predominantly produced by the liver, a major storage site for selenium, and secreted in the plasma. The full-length glycoprotein contains a selenium-rich domain with nine selenocysteine residues, as well as a thioredoxin-like catalytic site with one selenocysteine residue. SEPP1 constitutes the major form of selenium transport to peripheral tissues (9). SEPP1 also functions as an antioxidant that protects cells from oxidative damage by enabling full activity of thioredoxin reductases and glutathione peroxidases through adequate supply of selenium to extrahepatic tissues (see Glutathione peroxidases). SEPP1 appears to be especially critical for selenium homeostasis in the brain and testes where apolipoprotein E receptor 2 (apoER2) facilitates the uptake of SEPP1. Megalin is another SEPP1-specific lipoprotein receptor that helps limit urinary selenium loss through SEPP1 re-uptake by the kidneys (10). Moreover, SEPP1 has been recently implicated in the regulation of glucose metabolism and insulin sensitivity (11).

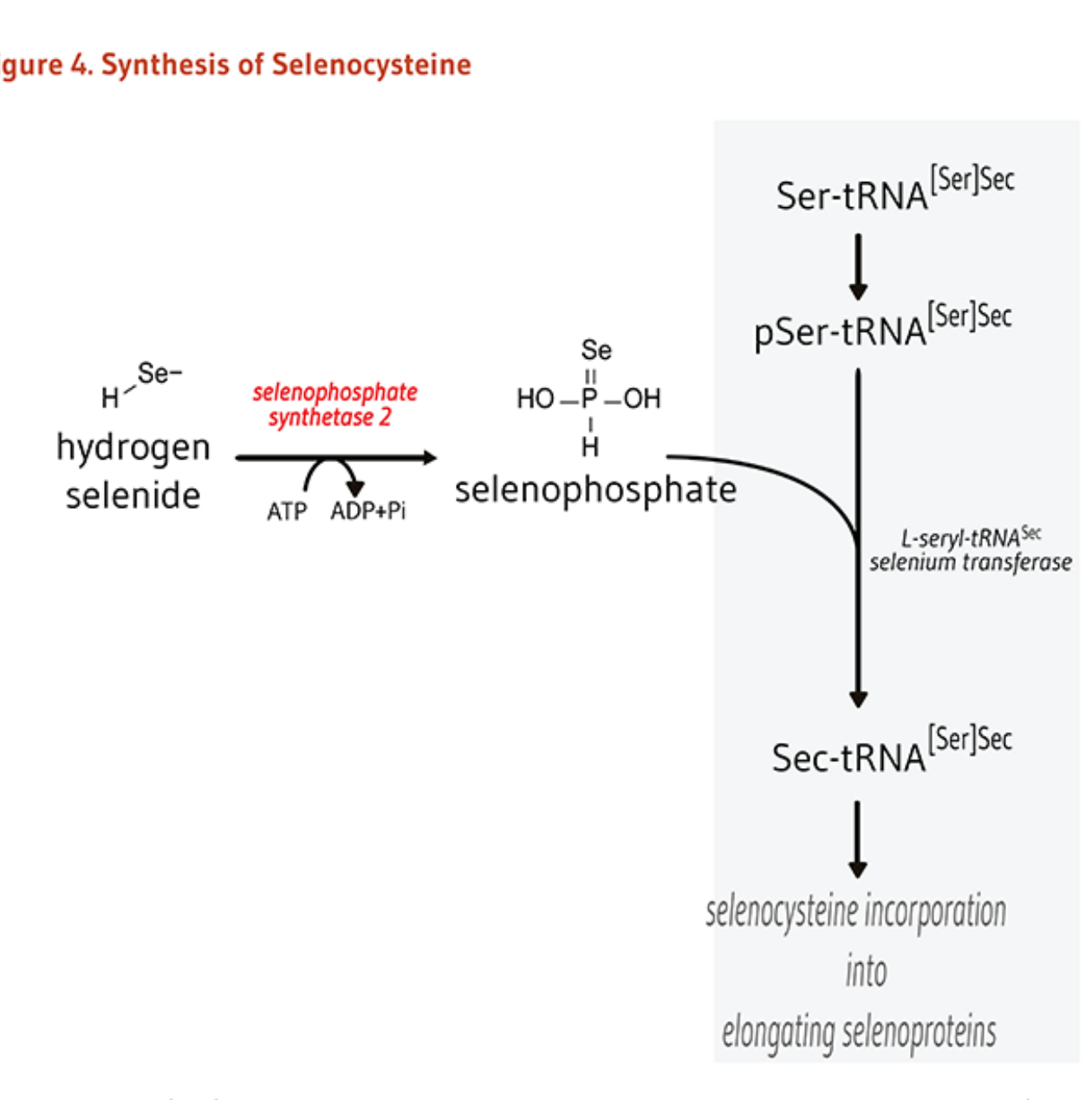
Selenoprotein W

Selenoprotein W (SEPW or SelW) exists in different isoforms (homologues) and is highly conserved across species. In humans, SEPW is expressed in numerous tissues, with highest levels found in skeletal muscle and heart (12). SEPW contains a selenocysteine residue and a cysteine residue that binds to a glutathione molecule, suggesting a role in redox regulation (13). The expression of SEPW is correlated with selenium status and appears to be sensitive to low-selenium supply (14, 15). SEPW expression in the brain has been found to confer protection against oxidative stress-induced neuronal cell death (16). SEPW also appears to be a negative regulator for 14-3-3 proteins. Indeed, 14-3-3 inhibition by SEPW in breast cancer cells was found to increase cell proliferation and cell survival through increasing resistance to genotoxic stress (17). In skeletal muscle cells, SEPW was shown to reduce the binding of 14-3-3 to TAZ, allowing TAZ translocation to the nucleus and subsequent activation of muscle cell differentiation genes (18). Finally, SEPW was found to prevent the degradation of the epidermal growth factor receptor (EGFR) in breast and prostate epithelial cells in culture. EGFR is constitutively activated in many tumors, and evidence of a role for SEPW in EGFR activation and signaling may help shed light on the relationship between selenium status and cancer risk (19).

Selenophosphate synthetase 2

There is no free pool of the amino acid selenocysteine in cells such that selenocysteine synthesis takes place on a specialized tRNA during the translation of selenoprotein mRNAs. The reaction is catalyzed by pyridoxal 5'-phosphate (PLP)-dependent L-seryl-tRNA^{Sec} selenium transferase and uses selenophosphate (monoselenium phosphate) as the selenium donor (**Figure 4**) (20). Selenophosphate synthetase 2 is a selenoenzyme that catalyzes the ATP-dependent synthesis of selenophosphate from hydrogen selenide (**Figure 4**) (3).

Figure 4. Synthesis of Selenocysteine


Ser-tRNA[Ser]Sec
pSer-tRNA[Ser]Sec
H Se−
hydrogen selenide
selenophosphate synthetase 2
ATP ADP+Pi
Se
HO–P–OH
H
selenophosphate
L-seryl-tRNASec selenium transferase
Sec-tRNA[Ser]Sec
selenocysteine incorporation into elongating selenoproteins

Selenocysteine (Sec) synthesis takes place on a special tRNA initially aminoacetylated (charged) with the amino acid serine (Ser). Ser-tRNA$^{[Ser]Sec}$ is then phosphorylated to produce pSer-tRNA$^{[Ser]Sec}$. Pyridoxal 5'-phosphate (PLP)-dependent L-seryl-tRNA^{Sec} selenium transferase catalyzes the conversion of Ser-tRNA$^{[Ser]Sec}$ into Sec-tRNA$^{[Ser]Sec}$ using selenophosphate as selenium donor. Selenophosphate is synthesized from hydrogen selenide in a reaction catalyzed by the selenoenzyme selenophosphate synthetase 2. Selenocysteine is incorporated into elongating proteins during translation. *Se, selenium; Ser-tRNA, L-seryl-tRNA; Sec-tRNA, L-selenocysteinyl-tRNA.*

Methionine-R-sulfoxide reductase B1 (formerly selenoprotein R)

The methionine sulfoxide reduction system is involved in the protection against oxidative stress and is especially critical for the regeneration of proteins damaged by reactive oxygen species (ROS). Indeed, ROS can oxidize methionine residues (methionine sulfoxides) within proteins and potentially impair their activities. In humans, two stereospecific families of methionine sulfoxide reductases (MsrA and MsrB) are encoded by a single *MSRA* gene and three *MSRB* genes (*MSRB1-3*). MsrA catalyzes the reduction of the S-form of methionine sulfoxide; the R-form of methionine sulfoxide is reduced by MsrB1, 2, or 3. Only MsrB1 has been characterized as a selenoprotein with one selenocysteine residue in its catalytic site. MsrB1 appears to be involved in the redox regulation of certain proteins. In macrophages, reorganization of the actin cytoskeleton necessary for chemotaxis and phagocytosis requires MsrB1-dependent reduction of methionine-R-sulfoxide residues within actin (21). Studies using *MSR* gene inactivation in mice have also shown that methionine sulfoxide reduction is implicated in the regulation of the methionine cycle (reviewed in 22). Both the thioredoxin (Trx) and GSH-dependent glutaredoxin (Grx) antioxidant systems have been found to reduce methionine sulfoxide reductases *in vitro* and/or *in vivo* (see **Figure 2** above) (22).

15 kDa selenoprotein

15 kDa selenoprotein (selenoprotein 15; SEP15) is highly expressed in several tissues, including prostate, kidney, testes, liver, and brain (23). Although its function is not known, SEP15 was found to interact with the endoplasmic reticulum UDP-glucose:glycoprotein glucosyltransferase (UGGT), an enzyme involved in the quality control of glycoprotein folding (24, 25). Because SEP15 has a thioredoxin-like catalytic site, SEP15 is thought to either regulate UGGT activity or the redox state of UGGT substrates (26). Mice lacking a functional SEP15 were found to develop nuclear cataract (lens opacification) at a very early age suggesting that SEP15 may be critical to the quality control system of protein folding in the lens (27). SEP15 may also be implicated in anticancer mechanisms (reviewed in 28).

Selenoprotein S

The mammalian selenoprotein S (known as SEPS1, SelS, or VCP-interacting membrane selenoprotein [VIMP]) is an endoplasmic reticulum (ER) membrane protein. SEPS1 is involved in the cellular response to ER stress (ER-associated degradation; ERAD) activated by the detection of misfolded proteins. SEPS1 contributes to the removal and transfer (retrotranslocation) of misfolded proteins from the ER lumen to the cytosol where proteins are tagged with ubiquitin before being degraded. A polymorphism or variation in the sequence within an ER-response element located in the *SEPS1* promoter was found to result in reduced *SEPS1* promoter activity and gene expression (29). The polymorphism corresponding to the substitution of a guanine (G) by an adenine (A) at nucleotide -105 (-105G>A) has been associated with increased plasma levels of pro-inflammatory cytokines. In addition, a case-control study recently reported that the A allele was more prevalent in individuals affected by Hashimoto thyroiditis (HT) — a T-cell-mediated autoimmune disease resulting in the destruction of thyroid cells — than in healthy controls (30). Other associations between *SEPS1* polymorphism (including -105G>A) and susceptibility to various conditions, such as preeclampsia, coronary artery disease, or gastrointestinal cancers, strongly suggest a role for this selenoprotein in the regulation of inflammatory and immune responses (31-34).

Other less well-characterized selenoproteins, which are also localized in the ER lumen and/or membrane, include selenoproteins K, M, N, and T (35).

Nutrient interactions

Antioxidant nutrients

The importance of selenium to biological systems, and specifically to the cellular redox (pro-oxidant/antioxidant) balance, is derived from its presence as selenocysteine in the catalytic site of selenoproteins (see Function). Other minerals that are critical components of antioxidant enzymes include copper (as superoxide dismutase), zinc (as superoxide dismutase), and iron (as catalase). Selenium acts in synergy with the antioxidant vitamins, vitamin C (ascorbic acid) and vitamin E (α-tocopherol), by regenerating them from their oxidized forms and promoting maximal antioxidant protection (36-38).

Iodine

While iodine is an essential component of thyroid hormones, the selenium-containing iodothyronine deiodinases (DIOs) are enzymes required for the conversion of thyroxine (T_4) to the biologically active thyroid hormone, triiodothyronine (T_3) (see Function). DIO1 activity may also be involved in regulating iodine homeostasis (39). The selenoenzymes, glutathione peroxidases, also play a critical role in thyroid function because they catalyze the degradation of peroxides generated during thyroid hormone synthesis (8). The epidemiology of coexisting iodine and selenium deficiencies in central Africa, but not in China, has been linked to the prevalence of myxedematous cretinism, a severe form of congenital hypothyroidism accompanied by mental and physical retardation. Selenium deficiency may be only one of several undetermined factors that might exacerbate the detrimental effects of iodine deficiency (40). Interestingly, selenium deficiency in rodents was found to have little impact on DIO activities as it appears that selenium is being supplied in priority for adequate synthesis of DIOs at the expense of other selenoenzymes (8).

Deficiency

Insufficient selenium intake may negatively affect the activity of several selenium-responsive enzymes, including glutathione peroxidases (GPx1 and GPx3), iodothyronine deiodinases, selenoprotein W, and methionine-R-sulfoxide reductase B1 (MsrB1). Even when severe, isolated selenium deficiency does not usually result in obvious clinical illness. Yet, compared to subjects with adequate selenium status, selenium-deficient individuals might be more susceptible to additional physiological stresses (41). Prolonged selenium deficiency may likely contribute to Keshan and Kashin-Beck diseases (see below).

Individuals at increased risk of selenium deficiency

Selenium deficiency has been reported in chronically ill patients who were receiving total parenteral nutrition (TPN) without added selenium for prolonged periods of time. Muscular weakness, muscle wasting, and cardiomyopathy (inflammation and damage to the heart muscle) have been observed in these patients. Nowadays, TPN solutions are routinely supplemented with selenium. The risk of selenium deficiency may be increased following bariatric surgery or in severe gastrointestinal conditions, such as Crohn's disease. Some specialized medical diets like those used to treat certain metabolic disorders, including phenylketonuria, homocystinuria, and maple syrup urine disease, need to be supplemented with selenium to ensure optimum selenium status in patients (42).

Keshan disease

Keshan disease is a fatal form of dilated cardiomyopathy that was first described in young women and children in a selenium-deficient region in China. The acute form of the disease is characterized by the sudden onset of cardiac insufficiency, while the chronic form results in moderate-to-severe heart enlargement with varying degrees of cardiac insufficiency (43). The incidence of Keshan disease is closely associated with very low dietary intakes of selenium and poor selenium nutritional status. Selenium supplementation (in the form of sodium selenite; Na_2SeO_3) was found to protect people from developing Keshan disease but could not reverse heart muscle damage once it had occurred (43). A recent case-control study reported that selenium-responsive glutathione peroxidase 1 (GPx1) activity was significantly lower in Keshan patients compared to healthy individuals. Interestingly, a specific *GPX1* polymorphism resulting in a proline-to-leucine transition at position 198 (Pro198Leu) is associated with a reduction in GPx1 activity and found to be more prevalent in Keshan patients. This *GPX1* polymorphism might confer a greater susceptibility to Keshan disease in carriers with low selenium nutritional status (44).

While selenium deficiency is a major etiological factor of Keshan disease, the seasonal and annual variation in disease occurrence suggested that other factors, especially an infectious agent, might be involved in addition to selenium deficiency (45). Coxsackie virus B3 is one virus type that has been isolated from Keshan patients, and animal studies have shown that this virus was capable of causing an inflammation of the heart (myocarditis) in selenium-deficient mice. Studies in mice also indicated that oxidative stress induced by selenium deficiency could result in changes in the viral genome, such as to convert a relatively harmless strain of coxsackie virus B3 into a myocarditis-causing strain (43). Although not proven in Keshan disease, it is possible that selenium deficiency may increase the virulence of viruses with the potential to invade and damage the heart muscle (46).

Kashin-Beck disease

Kashin-Beck disease (KBD) is another endemic condition that affects an estimated 2.5 million people in Tibet, northern and central China, North Korea, and southeastern Siberia (47). KBD is characterized by the degeneration of articular cartilage between joints (osteoarthritis) that can result in joint deformities and dwarfism in the most severe forms of the disease. The disease affects children as young as two years old. As with Keshan disease, KBD is prevalent in selenium-deficient provinces and thus generally affects people with very low selenium intakes (47). Recent studies have suggested that increased susceptibility to KBD in selenium-deficient populations might result from a reduced antioxidant protection associated with polymorphisms in *GPX* genes (48, 49). Yet, the etiology appears to be multifactorial, as a number of other causative factors have been suggested for KBD, including fungal toxins in grain, iodine deficiency, and contaminated drinking water (43).

Recent meta-analyses of a few small trials and prospective cohort studies have indicated that improving selenium nutritional status in children living in endemic areas may help reduce KBD incidence (50). Also, there is limited evidence to suggest that selenium supplementation could be useful in the treatment of patients with KBD. A meta-analysis of 10 randomized controlled trials reported a significant increase in the repairing rate of bone lesions in KBD children supplemented with sodium selenite for at least one year (51). Larger trials of higher quality are needed to assess whether selenium supplementation could result in disease remission.

The Recommended Dietary Allowance (RDA)

The dietary reference intakes (DRIs) for selenium were last revised in 2000 by the Food and Nutrition Board (FNB) of the US Institute of Medicine. The most recent RDA is based on the estimated average requirement (EAR) needed to maximize antioxidant enzyme glutathione peroxidase (GPx) activity in plasma (52).

Table 1. Recommended Dietary Allowance (RDA) for Selenium

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	15 (AI)	15 (AI)
Infants	7-12 months	20 (AI)	20 (AI)
Children	1-3 years	20	20
Children	4-8 years	30	30
Children	9-13 years	40	40
Adolescents	14-18 years	55	55
Adults	19 years and older	55	55
Pregnancy	all ages	-	60
Breast-feeding	all ages	-	70

Of note, the third National Health and Nutrition Examination Survey (NHANES III) reported that over 99% of the US participants had serum selenium concentrations consistent with selenium requirements being met (52), suggesting selenium supplementation is not needed for Americans.

Disease Prevention

Cancer

Animal studies

There has been considerable research on the effect of selenium supplementation on the incidence of cancer in animals. More than two-thirds of over 100 published studies in 20 different animal models of spontaneous, viral, and chemically induced cancers found that selenium supplementation (to at least adequate intake levels) significantly reduces tumor incidence, especially in comparison to selenium-deficient diets (53). Evidence of cancer-inhibiting effects of selenium has provided a strong rationale for investigating potential associations between selenium intake and cancer risk in humans.

Observational studies

Most of the early epidemiological evidence from case-control and nested case-control studies suggested either null or inverse associations between selenium exposure and risk of site-specific cancers (54). Markers of selenium exposure include toenail and blood selenium content, as well as plasma glutathione peroxidase (GPx) activity. However, it is not clear whether they adequately reflect selenium exposure from dietary and supplemental sources (see Sources) or selenium distribution in tissues and organs that may be affected by cancer. In the Danish Prospective Diet, Cancer, and Health prospective study that followed over 57,000 men and women for 14 years, the risk of rectal cancer was found to be 42% higher in current smokers compared to nonsmokers. No difference between smokers and nonsmokers regarding supplemental and dietary intakes of antioxidant micronutrients, including selenium, was found to contribute to the association of smoking and rectal cancer (55). Yet, because studies have consistently reported lower blood selenium concentrations and GPx activities in smokers compared to nonsmokers (reviewed in 56), estimation of selenium intakes might not be a reliable marker of selenium exposure in this population. Also, the chemical forms of selenium found in food are varied (see Sources) and may have very different biological and toxicological effects (57, 58).

A recent Cochrane review included 55 completed observational studies — mostly with a nested case-control design — published over three decades (54). A meta-analysis of 16 of these observational studies, including over 144,000 individuals, reported that higher versus lower selenium status was associated with a 31% lower risk of cancer at any site and a 40% lower risk of cancer-related mortality. A significantly lower risk was reported for bladder cancer (5 studies) and prostate cancer (17 studies); however, higher selenium status was not inversely associated with risks of breast cancer (8 studies), lung cancer (12 studies), colorectal cancer (5 studies), and gastric cancer (5 studies) (54). Another meta-analysis of 16 observational studies reported an inverse relationship between breast cancer and serum selenium concentrations (59). Gender differences in cancer susceptibility have been reported in some studies, although consistent evidence of different effects in men and women appears to be lacking.

Single nucleotide variations (polymorphisms) in the sequence of genes can modify gene expression level and the stability and activity of the synthesized proteins. For example, a proline-to-leucine transition caused by a specific polymorphism in the *GPX1* gene (rs1050450 C>T) is associated with reduced GPx1 enzymatic activity. The description of several polymorphisms in genes encoding selenoproteins has led to evaluation of possible associations with selenium status and cancer incidence. Notably, certain polymorphisms in genes coding for selenoproteins have been associated with increased risks of gastric and colorectal cancers (reviewed in 60). Additionally, a number of studies have investigated the effect of selenoprotein polymorphisms on the relationship between selenium status and prostate cancer risk. A nested case-control study within the EPIC-Heidelberg cohort has combined genotyping for several selenoprotein variants with markers of selenium status (61). Briefly, the study showed that a *GPX1* gene polymorphism (rs1050450 C>T) affected the association between selenium concentrations and prostate cancer risk. Specifically, selenium concentrations were found to be inversely associated with prostate cancer risk only among carriers of the *GPX1 T* allele. Additional variants in selenoprotein genes may mitigate the effect of selenium status on the risk of prostate cancer (62, 63). In another nested case-control study within the Physicians' Health Study (PHS), individuals in the highest versus lowest quartile of selenium concentrations were found to have a reduced risk of prostate cancer-related mortality except if carrying a specific variant in 15kDa selenoprotein gene (*SEP15* rs561104 G>A) (64). More research is needed to further unravel the mechanisms underlying the influence of gene-diet interactions on the risk of developing cancer.

Intervention trials

Community-based studies: A very early intervention study of selenium supplementation was undertaken in China among a general population of 130,471 individuals living in a high-risk area for viral hepatitis B infection and liver cancer. The trial provided table salt enriched with sodium selenite to the population of one township (20,847 people) using four other townships as controls. During an eight-year follow-up period, the average incidence of liver cancer was reduced by 35% in the selenium-supplemented population, while no reduction was found in the control populations. In a clinical trial in the same region, 226 individuals with evidence of chronic hepatitis B infection were supplemented daily with either 200 μg of selenium in the form of a selenium-enriched yeast tablet or a placebo yeast tablet. During the 4-year follow-up period, 7 out of 113 individuals on the placebo developed primary liver cancer, while none of the 113 subjects supplemented with selenium developed liver cancer (65).

Randomized controlled trials: The double-blind, placebo-controlled Nutritional Prevention of Cancer (NPC) study in 1,312 older adults with a history of nonmelanoma skin cancer found that supplementation with 200 μg/day of selenium-enriched yeast (selenized yeast) for an average of 7.4 years resulted in a 52% decrease in prostate cancer incidence in men (reviewed in 66). The protective effect of selenium supplementation was greatest in men with lower baseline plasma selenium and prostate-specific antigen (PSA) levels. A reduced incidence in lung, colorectal, and total cancer was also associated with supplementation with 200 μg/day (67) but not with 400 μg/day of selenium-enriched yeast (68). Besides, selenium supplementation increased the risk of one type of skin cancer (squamous cell carcinoma) by 25%. A larger randomized, placebo-controlled intervention trial (the SELECT study) in more than 35,000 middle-aged and selenium-replete men, randomized to receive selenium (in the form of selenomethionine, 200 μg/day) and/or vitamin E supplementation, was halted because of concerns regarding an increased risk of type 2 diabetes with selenium and increased risk of prostate cancer with vitamin E (69, 70). In addition, the supplementation of selenium, alone or together with vitamin E, did not show any benefits regarding the risk of prostate, lung, or colorectal cancers after 5.5 years of follow-up (71, 72). Outcomes from other smaller trials (reviewed in 66) also suggested either a lack of an effect or the possibility of an increased risk of cancer. The lack of a beneficial effect of selenium supplementation was supported in a recent meta-analysis of randomized controlled trials (54).

Cardiovascular disease

Low activity levels of the selenoenzymes, glutathione peroxidases (GPx), have been reported in oxidative stress-related diseases, including cardiovascular disease (CVD) (73). Theoretically, the maintenance of an optimal selenium status has the potential to protect against oxidative stress (including lipid peroxidation) and could eventually prevent chronic inflammation and cardiovascular disorders. Yet, analyses of cross-sectional data from 13,887 US adults included in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) failed to show any significant associations between serum selenium concentrations and mortality from CVD, coronary artery/heart disease (CAD), or stroke (74). In addition, while individuals with renal insufficiency are at higher risk of developing CAD compared to those with normal kidney function, that risk was not found to be greater with low rather than normal selenium concentrations in serum (≤98 ng/mL vs. >98 ng/mL) (75).

A cross-sectional study based on NHANES 2003-2004 data from 2,638 participants ages 40 years and over found that the risk of high blood pressure (hypertension), a major contributing factor for CVD, was 73% higher in individuals in the upper versus lowest quintile of serum selenium concentrations (≥150 ng/mL vs. <122 ng/mL) (76). Yet, a recent systematic review of the literature failed to find enough evidence to support any relationship between serum selenium concentrations and hypertension (77). Besides, a few observational studies have also reported associations between normal-to-high selenium status and elevated serum lipid levels in selenium-replete populations, speculating that selenium might interfere with lipid metabolism and adversely affect cardiovascular health (78, 79). At present, randomized controlled trials have not provided consistent results regarding the effect of selenium supplementation on lipid levels nor have they demonstrated any additional cardiovascular benefits of selenium in individuals with suboptimal or optimal selenium intakes (80).

Disease Treatment

Immune dysfunction

Selenium deficiency has been associated with impaired immunity and chronic inflammation (81). A considerable amount of research conducted in cell culture and animal models indicates that selenium plays essential roles in regulating the migration, proliferation, differentiation, activation, and optimal function of immune cells, thus influencing innate immunity, B-cell dependent antibody production, and T-cell immunity (reviewed in 82). Recent evidence on the role of selenium and selenoproteins in the production of lipid mediators (called eicosanoids) involved in inflammatory responses suggests that selenium supplementation might mitigate dysfunctional inflammatory responses that contribute to the pathogenesis of many chronic health conditions (83). At present, randomized controlled trials are needed to evaluate the potential benefits of selenium supplementation in inflammatory disorders, such as asthma (84) and inflammatory bowel disease (85).

Infectious diseases

HIV/AIDS

In areas of widespread malnutrition, deficiencies in micronutrients (including selenium) are common in individuals infected by the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS). Before antiretroviral therapy (ART) became the standard for HIV treatment, observational studies had consistently reported associations between low serum selenium concentrations and HIV infection in well-nourished subjects (86). Poor selenium status has been linked to increased risks of dilated cardiomyopathy and mortality in HIV-infected children and adults, as well as mother-to-child HIV transmission and perinatal mortality (reviewed in 87. Early laboratory studies have suggested that HIV might disrupt normal antioxidant defenses in infected T-cells by reducing the levels of selenoproteins, i.e., thioredoxine reductases and glutathione peroxidases (87). Interestingly, a recent cross-sectional study found that HIV-seropositive individuals receiving ART for more than two years had undetectable plasma viral loads, higher CD4 lymphocyte T-cell counts, and adequate serum selenium concentrations compared to ART-naïve subjects (88). Because the antioxidant activity of selenoproteins may interfere with viral replication in HIV-infected immune cells (89,90), it has been suggested that selenium supplementation might serve as a potential adjunct to ART for HIV patients.

A few trials of selenium supplementation in HIV-infected individuals have been conducted. A randomized, double-blind, placebo-controlled trial in 186 HIV-positive adults initially found that selenium supplementation at 200 μg/day for two years significantly decreased the rate of hospital admissions (91). Another randomized, double-blind, placebo-controlled trial in 174 HIV-positive individuals reported that 200 μg/day of selenium supplementation (in the form of selenium-enriched yeast) for nine months increased serum selenium concentrations, improved CD4 lymphocyte T-cell count, and prevented any progression of the HIV viral load (92). In a third double-blind trial in Tanzania, 913 pregnant women between 12 and 27 weeks' gestation were randomized to receive 200 μg/day of selenium (as selenomethionine) or a placebo until six months after birth. Selenium supplementation had no effect on maternal CD4, CD8, and CD3 T-cell counts and on HIV viral load, but it significantly decreased the risk of acute or persistent diarrhea (93, 94). In addition, the risk of death between six weeks and six months postpartum was significantly reduced in infants of mothers supplemented with selenium compared to placebo (94).

A recent four-armed trial in Botswana randomized 878 HIV-positive adults at an early stage of the infection to receive either a placebo treatment, multivitamins (vitamins B, C, and E), 200 μg/day of selenium, or both multivitamins and selenium for 24 months (95). Unlike selenium alone, supplementation with multivitamins (with or without selenium) reduced the risk of immune decline by significantly increasing the time before ART initiation became necessary (i.e., when CD4 T-cell count fell below 251 cells/mcL) compared to placebo. In the study, a combined outcome of (1) CD4 T-cell count falling below 251 cells/mcL; (2) occurrence of AIDS-defining conditions; and (3) AIDS-related death — whichever happened first — was used to evaluate disease progression in the different arms of treatment. Compared to placebo, there was a longer period of time from randomization to the date of the composite outcome in individuals supplemented with multivitamins plus selenium, but not in those who received multivitamins or selenium alone (95). More research is needed to replicate these preliminary results, especially in settings and communities where malnutrition hastens the progression of HIV infection and access to antiretroviral therapy may be limited.

Sepsis

The systemic inflammatory response syndrome (SIRS) results from a systemic inflammatory response that can be due to an infection (sepsis) (96). Severe sepsis and septic shock — defined as persistent sepsis-induced low blood pressure — are associated with elevated mortality rates in critically ill patients (96, 97). Because systemic inflammatory responses involve excessive oxidative stress, it has been suggested that providing antioxidant nutrients like selenium may improve the outcome of critically ill patients in intensive care units. Two recent meta-analyses of randomized controlled trials found that intravenous selenium supplementation (as sodium selenite) in critically ill patients with SIRS, sepsis, or septic shock resulted in significantly reducing the risk of mortality by 17% to 27% (98, 99). More trials are needed to identify the appropriate schedule of selenium administration (in terms of dose, route, and treatment duration) and to assess additional outcomes (e.g., infectious complications and length of hospital stay).

Autoimmune thyroid diseases

Hashimoto thyroiditis (HT; chronic autoimmune thyroiditis) is an autoimmune disease characterized by T-cell infiltration in the thyroid gland and circulating autoantibodies (predominantly raised against thyroid peroxidase), causing prolonged inflammation, tissue damage, and hypothyroidism (8). While the function of the thyroid gland of healthy individuals is usually protected from variations in selenium supply, selenium deficiency and genetic polymorphisms affecting the activity of selenoproteins might be potential contributing factors to autoimmune thyroid diseases. A recent systematic review (100) identified four randomized controlled trials that evaluated the effect of selenium supplementation as an adjunct treatment to T_4 replacement therapy (levothyroxine) in HT patients (101-104). While three out of four studies suggested a reduction in levels of circulating autoantibodies, none of them provided information on whether selenium may improve mood- and health-related symptoms to allow for a decreased dosage of levothyroxine. Another randomized controlled trial found that selenium supplementation improved the well being of patients affected by another autoimmune thyroid disease leading to hyperthyroidism (Graves disease) (105). The results of two ongoing, randomized, placebo-controlled trials — the CATALYST in HT patients and the GRASS trial in patients with Graves disease — may provide insight into an effect of selenium on thyroid-specific quality-of-life criteria and inform clinical decision making (106, 107).

Sources

Food sources

The richest food sources of selenium are organ meats and seafood, followed by muscle meats. Drinking water is not considered to be a significant source of selenium in North America. However, in areas, where high levels of selenium in soil contribute to the selenium content of the water, higher levels of selenium may be found in wells used for drinking water (108). In general, there is wide variation in the selenium content of plants and grains, especially because some plants, including garlic, Brazil nuts, and multiple *Brassica* species, tend to accumulate selenium ('selenium accumulators'), while other assimilate selenium to a lesser extent ('non-accumulators'). The assimilation of selenium by plants also depends on soil selenium content. Brazil nuts grown in areas of Brazil with selenium-rich soil may provide more than 100 μg of selenium in one nut, while those grown in selenium-poor soil provide 10 times less (109). In the US, grains are a good source of selenium, but fruit and vegetables tend to be relatively poor in selenium.

Various chemical forms (species) of selenium are found in selenium accumulators, including selenate (inorganic selenium), selenomethionine, selenocysteine, selenium-methyl-selenocysteine, and γ-glutamyl-selenium-methyl-selenocysteine. Although the two latter compounds are predominant in plants of the *Allium* and *Brassicaceae* families (which include garlic, onion, and broccoli), wheat, other grains (including Brazil nuts), and soy are rich in selenomethionine and contain smaller amounts of selenocysteine and selenate. Less is known about selenium species and distribution in dietary sources of animal origin. Animal nutrition and growth conditions certainly contribute to the selenium species formed and their relative quantities, and it is assumed that the metabolic pathway of dietary selenium in animals is similar to that in humans. Selenocysteine is predominantly formed in animals fed inorganic selenium, while selenomethionine is derived from dietary sources of plant origin (reviewed in 110).

In the US, the national survey NHANES III reported mean dietary intakes ranging between 100.5 μg/day and 158.5 μg/day in adults ages 19-50 years (52). **Table 2** lists some good food sources of selenium and their selenium content in micrograms (μg). For more information on the selenium content of specific foods, search USDA's FoodData Central.

Table 2. Some Common Food Sources of Selenium

Food	Serving	Selenium (μg)
Brazil nuts (from selenium-rich soil)	1 ounce (6 kernels)	543.5*
Tuna (yellowfin, cooked, dry heat)	3 ounces	92.0
Oysters (Pacific, raw)	3 ounces	65.4
Clams (mixed, cooked, steamed)	3 ounces	54.4
Halibut (Atlantic and Pacific, cooked, dry heat)	3 ounces	47.1
Shrimp (cooked, steamed)	3 ounces	42.1
Salmon (Chinook, cooked, dry heat)	3 ounces	39.8
Noodles (egg, cooked, enriched)	1 cup	38.2
Crab (queen, cooked, steamed)	3 ounces	37.7
Pork (lean, tenderloin, cooked, roasted)	3 ounces	32.5
Beef (lean, plate steak, cooked, grilled)	3 ounces	30.6
Chicken (light-meat, cooked, roasted)	3 ounces	25.8
Rice (brown, long-grain, cooked)	1 cup	19.1
Sunflowers seed kernels (dried)	¼ cup	18.6
Whole-wheat bread	2 slices	16.4
Milk (fat free or skim)	8 fluid ounces (1 cup)	7.6
*Above the tolerable upper intake level (UL) of 400 μg/day.		

Supplements

Selenium supplements are available in several forms. Sodium selenite and sodium selenate are inorganic forms of selenium. Sodium selenate is almost completely absorbed, but a significant amount is excreted in the urine before it can be incorporated into proteins. Sodium selenite is only about 50% absorbed but is better retained than selenate once it is absorbed. Selenomethionine is about 90% absorbed (52); however, only about 34% may then actually be converted to free selenomethionine (111). Selenomethionine and selenium-enriched yeast, which mainly supply selenomethionine, are also available as supplements. The consumer should be aware that some forms of selenium-enriched yeast on the market contain yeast plus mainly inorganic forms of selenium.

Although both inorganic and organic forms of selenium can be metabolized to selenocysteine by the body and incorporated into selenoenzymes, they may not equally contribute to the maintenance of an adequate selenium status. In intervention trials, supplementation with an organic form of selenium (selenomethionine) more effectively increased blood selenium concentrations compared to supplementation with inorganic forms (i.e., sodium selenite and sodium selenate) (110). Yet, inorganic forms may increase plasma glutathione peroxidase (GPx) activity more effectively than organic forms (reviewed in 112). It has also been suggested that the incorporation of selenomethionine in place of methionine into tissue proteins may ensure that selenium is available upon protein turnover (110).

Selenium-enriched foods

Selenium-enriched foods have been of interest to scientists, especially because of the suggestion that some of the chemical forms of selenium produced by plants might be more potent modifiers of cancer risk than those currently available in supplements. Although there is currently no evidence of long-term health benefits associated with the consumption of selenium-enriched foods, results from animal studies and intervention trials suggest that protein-based sources of selenium are more effective at increasing GPx activity than selenium-enriched yeast and selenomethionine (112). Food fortification may also represent a cost-effective strategy to improve selenium nutritional status in populations at risk of inadequacy (113).

Safety

Toxicity

Although selenium is required for health, high doses of selenium can be toxic. Acute and fatal toxicities have occurred with accidental or suicidal ingestion of gram quantities of selenium. Clinically significant selenium toxicity was reported in 13 individuals after taking supplements that contained 27.3 mg (27,300 μg) per tablet due to a manufacturing error. Chronic selenium toxicity (selenosis) may occur with smaller doses of selenium over long periods of time. The most frequently reported symptoms of selenosis are hair and nail brittleness and loss. Other symptoms may include gastrointestinal disturbances, skin rashes, a garlic breath odor, fatigue, irritability, and neurologic disorders. In an area of China with a high prevalence of selenosis, toxic effects occurred with increasing frequency when blood selenium concentrations reached a level corresponding to an intake of 850 μg/day.

The Food and Nutrition Board (FNB) of the US Institute of Medicine set the tolerable upper intake level (UL) for selenium at 400 μg/day in adults based on the prevention of hair and nail brittleness and loss and early signs of chronic selenium toxicity (52). The UL of 400 μg/day for adults includes both selenium obtained from food and selenium from supplements (**Table 3**).

Table 3. Tolerable Upper Intake Level (UL) for Selenium

Age Group	UL (μg/day)
Infants 0-6 months	45
Infants 6-12 months	60
Children 1-3 years	90
Children 4-8 years	150
Children 9-13 years	280
Adolescents 14-18 years	400
Adults 19 years and older	400

Do selenium supplements increase the risk for type 2 diabetes mellitus?

A few studies have examined the relationship between selenium status and type 2 diabetes mellitus. In the cross-sectional analysis of NHANES III (1988-1994) data from 8,876 adult participants, the highest versus lowest quintile of serum selenium concentrations (≥137 ng/mL vs. <111 ng/mL) was associated with an increased risk of type 2 diabetes (114). Data analyses from 917 participants (≥40 years of age) of NHANES 2003-2004 also indicated an increased prevalence of type 2 diabetes in the highest versus lowest quartile of serum selenium concentrations (≥147 ngm/L vs. <124 ng/mL). Individuals in the highest versus lowest quartile of serum selenium concentrations also had higher levels of plasma glucose and glycated hemoglobin, suggestive of poor glycemic control (115). The randomized, double-blind, placebo-controlled study in 1,312 participants in the Nutritional Prevention of Cancer (NPC) trial found that selenium supplementation (200 μg/day; mean follow-up of 7.7 years) significantly increased the risk for type 2 diabetes in participants in the highest tertile of baseline plasma selenium concentrations (116). In addition, in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), more cases of type 2 diabetes were found in the selenium group (200 μg/day; median follow-up of 5.5 years) than in the placebo group, but this was only a trend and not statistically significant (72).

At present, the mechanisms behind these observations are not well understood. An increase in insulin sensitivity has been reported in individuals with congenital (inborn) deficiency of most selenoproteins (117). Results from several animal studies also indicated that selenium supplementation and selenoproteins may interfere with insulin action and glucose homeostasis (reviewed in 118). On the other hand, recent studies have found that impaired glucose metabolism in patients with type 2 diabetes may affect SEPP1 expression and selenium homeostasis (11, 119, 120). While more research is needed to fully understand the interplay between carbohydrate metabolism and selenium homeostasis, the use of selenium supplements is considered unlikely to increase the risk of type 2 diabetes in healthy individuals but should be discouraged in those with high selenium status and/or at increased risk for developing type 2 diabetes (118).

Drug interactions

At present, few interactions between selenium and medications have been reported (121). For example, the anticonvulsant drug valproic acid and the chemotherapeutic agent cisplatin may lower circulating selenium concentrations in treated subjects (122, 123). Also, supplemental sodium selenite was found to reduce the toxicity of the antibiotic nitrofurantoin and the herbicide paraquat in animal studies (124).

Antioxidant supplements and statins

A three-year randomized controlled trial in 160 patients with documented coronary artery disease (CAD) and low high-density-lipoprotein (HDL) levels found that a combination of simvastatin (Zocor) and niacin increased HDL2 subfraction levels, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events (125). Surprisingly, when an antioxidant combination (1,000 mg of vitamin C, 800 IU of vitamin E (*d*-α-tocopherol), 100 μg of selenium, and 25 mg of β-carotene daily) was taken with the simvastatin-niacin combination, the protective effects were diminished. However, the individual contribution of selenium cannot be established, and other studies have reported that antioxidant vitamins alone could interfere with the action of HDL-raising drugs, including statins (126).

Linus Pauling Institute Recommendation

The average American diet is estimated to provide about 100 μg/day of selenium, an amount that is well above the current RDA (55 μg/day) and appears sufficient to optimize plasma and cellular glutathione peroxidase (GPx) activity. A recent 10-week randomized controlled study in healthy British adults (ages, 50-64 years) estimated that about 105 μg/day of total selenium intake was required to maximize the plasma concentrations of selenoprotein P (SEPP1), another useful biomarker of selenium status (127). However, a similar trial in an American cohort with higher baseline plasma selenium concentrations found no effect of selenium supplementation on SEPP1 concentrations (128). While the amount of selenium in multivitamin/mineral (MVM) supplements varies considerably, MVM supplements rarely provide more than the Daily Value (DV) of 70 μg. Eating a varied diet and taking a daily MVM supplement should provide sufficient selenium for most people in the US and help improve selenium status in populations with lower selenium intakes outside the US.

Men

At present, the effect of selenium supplementation on cancer risk is not clear enough to support a general recommendation for an extra selenium supplement, especially in men with serum selenium concentrations consistent with adequate selenium intakes. The SELECT trial found that 200 μg/day of selenium did not reduce the risk of prostate cancer (72), refuting the results of the NPC trial (see Cancer). Another recent multicenter, randomized, double-blind, placebo-controlled trial (the Negative Biopsy Trial) in 699 men at high risk of prostate cancer found no effect of either 200 μg/day or 400 μg/day of selenium on prostate cancer risk during a mean follow-up of 36 months (129). In addition, because current evidence suggests a U-shaped relationship between selenium status and prostate cancer risk (130), men should avoid taking supplemental selenium that would exceed 200 μg/day.

Women

At present, there is no clinical evidence showing that selenium supplementation above recommended levels decreases the risk of breast cancer although some, but not all, observational studies have found an inverse relationship between selenium status and breast cancer in women (59).

Older adults (>50 years)

Aging has not been associated with significant changes in the requirement for selenium. A five-year, randomized, double-blind, placebo-controlled trial in healthy Danish older people (ages at inclusion, 60-74 years) found that selenium supplementation (100-300 μg/day) had little-to-no impact on circulating levels of antioxidant enzymes, including GPx (131).

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Sodium (Chloride)

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Summary

- Sodium and chloride — major electrolytes of the fluid compartment outside of cells (i.e., extracellular) — work together to control extracellular volume and blood pressure. Disturbances in sodium concentrations in the extracellular fluid are associated with disorders of water balance. *(More information)*
- Various mechanisms act on the kidney to ensure that the amount of sodium lost via renal excretion compensates adequately for the amount of sodium consumed, thereby maintaining sodium homeostasis. *(More information)*
- Hyponatremia (abnormally low sodium concentrations in blood) is common among older adults and in individuals with hypertension, kidney disease, and heart disease. Hyponatremia also occurs in up to 30% of hospitalized patients. *(More information)*
- Acute severe hyponatremia may lead to brain edema with neurologic consequences and be lethal if not promptly diagnosed and treated. Mild chronic hyponatremia with long-term adverse health effects, such as attention deficits, gait instability, falls, and bone loss and fractures, has been associated with cardiovascular morbidity and mortality. *(More information)*
- In 2019, the National Academy of Medicine established an adequate intake (AI) for sodium of 1.5 grams (g)/day in adults, equivalent to 3.8 g/day of sodium chloride (salt). *(More information)*
- The National Academy of Medicine established a Chronic Disease Risk Reduction Intake (CDRR) for sodium of 2.3 g/day (5.8 g/day of salt) for adults based on evidence of potential long-term health benefits on blood pressure and risk of hypertension and cardiovascular disease associated with reducing sodium intakes below this level. *(More information)*
- Current sodium intakes of the US adult population far exceed the CDRR. Sodium has been identified as a nutrient of public health concern for overconsumption. *(More information)*
- Excess dietary sodium is a major contributor to hypertension, which is a leading preventable risk factor for cardiovascular disease. Randomized controlled studies demonstrated that dietary sodium reduction (by 1.8 to 3.2 g/day) could lower blood pressure in subjects with elevated blood pressure. Yet, current evidence fails to support a decrease in cardiovascular morbidity and mortality with moderate sodium restriction in patients with hypertension. *(More information)*
- Additional adverse health outcomes, including gastric cancer, osteoporosis, and kidney stones, have also been linked to sodium overconsumption. *(More information)*

Salt (sodium chloride) is essential for life. Total body sodium in an average 70-kg person is of about 4,200 mmol (~100 g), of which 40% is found in bone and 60% in the fluid inside and outside of cells (1). Total body chloride averages 2,310 mmol (~82 g), of which 70% is distributed in the extracellular fluid and the remaining is found in the collagen of connective tissue (1). Multiple mechanisms work in concert to tightly regulate the body's sodium and chloride concentrations. Although this review emphasizes the function and requirements of sodium, sodium and chloride ions work together to control extracellular volume and blood pressure (1).

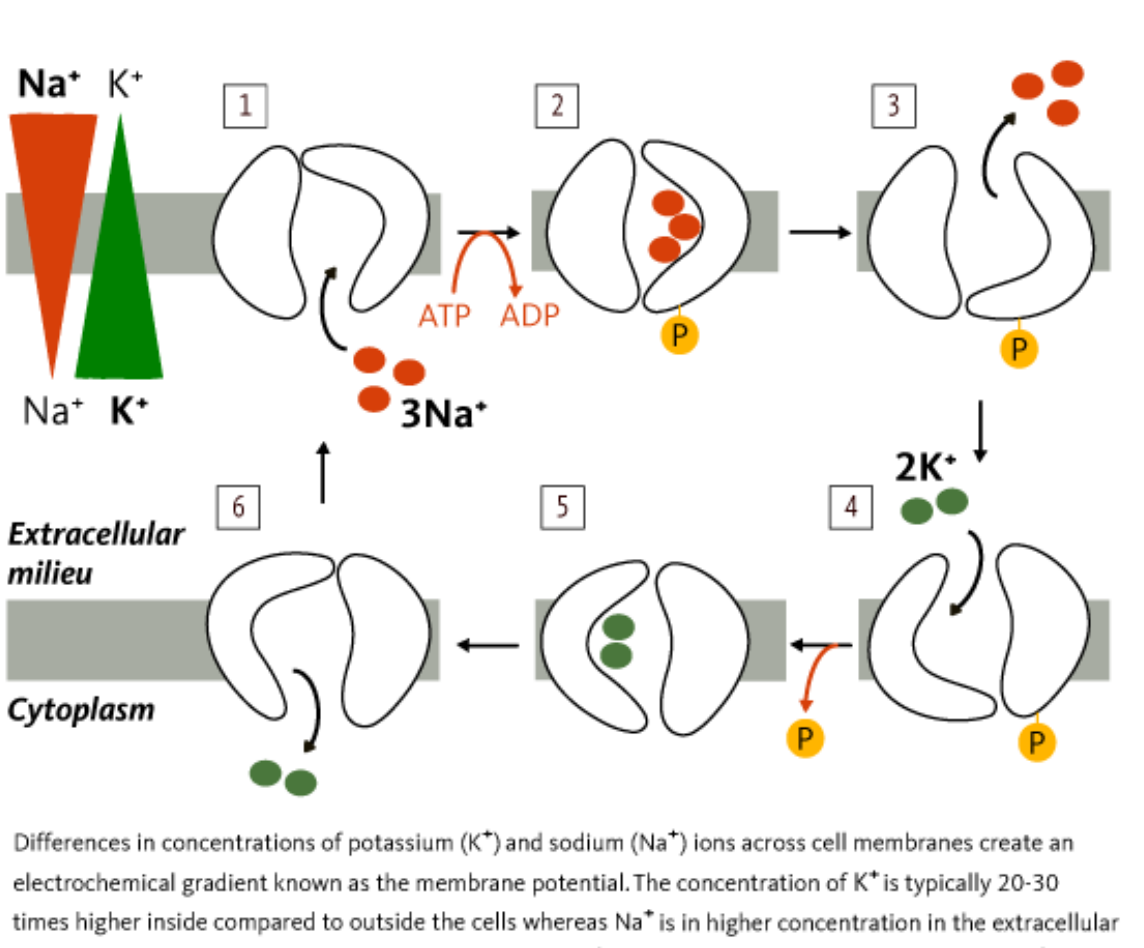
Function

Sodium (Na^+) and chloride (Cl^-) are the principal ions in the extracellular compartment, which includes blood plasma, interstitial fluid (fluid between cells), and transcellular fluid (e.g., cerebrospinal fluid, joint fluid). As such, they play critical roles in a number of life-sustaining processes.

Maintenance of membrane potential

Sodium and chloride are electrolytes that contribute to the maintenance of concentration and charge differences across cell membranes. Potassium (K^+) is the principal positively charged ion (cation) inside of cells, while sodium is the principal cation in extracellular fluid. Potassium concentrations are about 30 times higher inside than outside cells, while sodium concentrations are more than 10 times lower inside than outside cells. The concentration differences between potassium and sodium across cell membranes create an electrochemical gradient known as the membrane potential. A cell's membrane potential is maintained by ion pumps in the cell membrane, especially the Na^+/K^+ ATPase pumps. These pumps use ATP (energy) to pump sodium out of the cell in exchange for potassium (**Figure 1**). Their activity has been estimated to account for 20%-40% of the resting energy expenditure in a typical adult. The large proportion of energy dedicated to maintaining sodium/potassium concentration gradients emphasizes the importance of this function in sustaining life. Tight control of cell membrane potential is critical for nerve impulse transmission, muscle contraction, and cardiac function (2-4).

Figure 1. A Simplified Model of the Na^+/K^+ATPase Pump



Differences in concentrations of potassium (K^+) and sodium (Na^+) ions across cell membranes create an electrochemical gradient known as the membrane potential. The concentration of K^+ is typically 20-30 times higher inside compared to outside the cells whereas Na^+ is in higher concentration in the extracellular compared to the intracellular compartment. Therefore, K^+ diffuses easily out of the cells whereas Na^+ diffuses easily into the cells. The Na^+/K^+ ATPase pump is thus required to maintain the membrane potential by pumping Na^+ out of the cells and K^+ into the cells. In the presence of magnesium (Mg^{2+}), adenosine triphosphate (ATP) provides the energy to translocate 3 Na^+ ions and 2 K^+ ions across the plasma membrane against their concentration gradients. The binding of ATP and magnesium (Mg^{2+}) allows the enzyme to adopt a conformation that opens toward the cytoplasm for the binding and the translocation of Na^+ ions; In turn, the binding of K^+ ions induces the release of phosphate and Mg^{2+} and the translocation of K^+ ions to the cytoplasm.

[Figure 1 - Click to Enlarge]

Nutrient absorption and transport

Absorption of sodium in the small intestine plays an important role in the absorption of chloride, amino acids, glucose, and water. Similar mechanisms are involved in the reabsorption of these nutrients after they have been filtered from the blood by the kidneys. Chloride, in the form of hydrochloric acid (HCl), is also an important component of gastric juice, which aids the digestion and absorption of many nutrients (5).

Maintenance of blood volume and blood pressure

Because sodium is the primary determinant of extracellular fluid volume, including blood volume, a number of physiological mechanisms that regulate blood volume and blood pressure work by adjusting the body's sodium content. In the circulatory system, pressure receptors (baroreceptors) sense changes in blood pressure and send excitatory or inhibitory signals to the nervous system and/or endocrine glands to affect sodium regulation by the kidneys. In general, sodium retention results in water retention, and sodium loss results in water loss (6). Below are descriptions of three mechanisms contributing to a larger multifactorial homeostatic control system that governs blood volume and blood pressure through regulation of sodium balance. These regulatory mechanisms are especially important for the control of sodium transport in various segments of the nephron (basic structural unit of the kidney), including the proximal and distal convoluted tubules, the thick ascending limb of the loop of Henle, and the collecting duct.

Renin-angiotensin-aldosterone system

In response to a significant decrease in blood volume or pressure (e.g., serious blood loss or dehydration), the kidneys release renin into the circulation. Renin is an enzyme that splits a small peptide (angiotensin I) from a larger protein (angiotensinogen) produced by the liver. Angiotensin I is split into a smaller peptide (angiotensin II) by angiotensin converting enzyme (ACE), an enzyme present on the inner surface of blood vessels and in the lungs, liver, and kidneys. Angiotensin II stimulates the constriction of small arteries, resulting in increased blood pressure. Angiotensin II is also a potent stimulator of aldosterone synthesis by the adrenal glands. Aldosterone is a steroid hormone that acts on the kidneys to increase the reabsorption of sodium and the excretion of potassium. Retention of sodium by the kidneys increases the retention of water, resulting in increased blood volume and blood pressure (7).

Anti-diuretic hormone

Secretion of anti-diuretic hormone (ADH; also known as arginine vasopressin [AVP]) by the posterior pituitary gland is stimulated by a significant decrease in blood volume or pressure. In conjunction with the renin-angiotensin-aldosterone system, ADH stimulates epithelial sodium channels (ENaC) in apical cell membranes along kidney nephron distal tubules to increase the reabsorption of sodium and water (8).

Dopaminergic system

Dopamine is produced from L-DOPA in the kidney proximal tubules and acts on dopamine receptors distributed along the proximal tubules and the thick ascending limbs of the loop of Henle to regulate sodium transport. Dopamine promotes sodium excretion (natriuresis) by inhibiting the Na^+/H^+ exchanger and Na^+/phosphate (Pi) co-transporter in apical cell membranes and the Na^+/bicarbonate (HCO_3^-) co-transporter and Na^+/K^+ ATPase in basolateral cell membranes. The inhibitory effect of dopamine on Na^+/K^+ ATPase is enhanced by the natriuretic hormone, atrial natriuretic peptide (ANP), which is secreted by heart muscle cells into the circulation (9).

Deficiency

Hyponatremia, defined as a serum sodium concentration ($[Na^+]$) <136 mmol/liter (mM), may result from increased fluid retention (dilutional hyponatremia) or increased sodium loss. Inadequate sodium intakes rarely result in hyponatremia, even in those on very low-salt diets, because the kidneys increase the excretion of water in order to maintain serum osmolality (i.e., electrolyte-water balance). The results of the 1999-2004 US National Health And Nutrition Examination Survey (NHANES) indicated an overall prevalence of hyponatremia of 1.9% in a US population representative sample of 14,697 participants aged 18 and older (10). Hyponatremia was found to be more prevalent among older individuals (3.1% in those aged 65 to 84 years) and in those suffering from hypertension (2.9%), diabetes mellitus (3.3%), coronary heart disease (CHD; 2.6%), stroke (3.6%), chronic obstructive pulmonary disease (COPD; 3.9%), cancer (3.4%), and psychiatric disorders (2.9%) (10). Hyponatremia is also common in hospitalized patients, with an estimated 15%-30% having mild hyponatremia (serum $[Na^+]$: 130-135 mM) and up to 7% having moderate-to-severe hyponatremia (serum $[Na^+]$ <130 mM) (11).

Causes of hyponatremia

Dilutional hyponatremia may be due to inappropriate anti-diuretic hormone (ADH) secretion, which is associated with disorders affecting the central nervous system, and with use of certain drugs (see Drug interactions). In some cases, excessive water intake may also lead to dilutional hyponatremia (see also Exercise-associated hyponatremia). Conditions that increase the loss of sodium and chloride include severe or prolonged vomiting or diarrhea, excessive and persistent sweating, the use of some diuretics, and some forms of kidney disease. Too severe restriction of dietary sodium intake in renal patients with hypertension and congestive heart failure might also result in harmful body depletion of sodium (1).

Exercise-associated hyponatremia

Exercise-associated hyponatremia (EAH) is dilutional hyponatremia occurring in individuals competing in endurance (up to 6 h in duration) and ultra-endurance (>6 h in duration) exercise events, such as marathons, Ironman triathlons, mountain bike races, hiker treks, and open-water ultra-distance swimming events. Of note, symptomatic EAH has been increasingly reported in shorter events, such as half-marathons and sprint triathlons. The development of hyponatremia during or up to 24 h after intense and/or sustained physical activity has been linked to fluid overload due to excessive water intakes, impaired urinary water excretion due to persistent ADH secretion, and very low or very high ambient temperature (12). Risk factors include pre-exercise hyperhydration, use of non-steroidal anti-inflammatory drugs (NSAIDs), and prolonged exercise (>4 h) (reviewed in 12).

Signs and symptoms of hyponatremia

Symptoms of hyponatremia include headache, nausea, vomiting, muscle cramps, fatigue, disorientation, and fainting. Complications of severe and rapidly developing hyponatremia may include cerebral edema (swelling of the brain), seizures, coma, and brain damage. Acute or severe hyponatremia may be fatal without prompt and appropriate medical treatment (13).

Chronic mild hyponatremia has been associated with deficits in gait and attention, falls, and bone loss and fractures, especially in women and the elderly (14, 15). A recent 11-year prospective cohort study in over 3,000 men free of cardiovascular disease (CVD) also reported significantly higher risks of stroke, coronary heart disease, total CVD events, CVD-related mortality, and all-cause mortality in participants with mild-to-severe hyponatremia (serum $[Na^+]$ <139 mM) compared to those with serum $[Na^+]$ between 139 mM and 144 mM (16). In addition, in a meta-analysis of 81 observational studies in patients with diverse medical conditions (including cardiovascular disease, pulmonary infections, and cirrhosis), the risk of mortality was found to be nearly three times greater in hyponatremic compared to normonatremic subjects (17). Improvement or normalization of serum $[Na^+]$ in hyponatremic subjects was associated with a reduced mortality rate in patients with diverse clinical conditions (18).

Drug interactions

Table 1 lists some medications that may increase the risk of hyponatremia (10, 19).

Table 1. Medications that Increase the Risk of Hyponatremia

Medication Family	Examples
Diuretics	Hydrochlorothiazide, Furosemide (Lasix)
Non-steroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen (Advil, Motrin), Naproxen sodium (Aleve)
Opiate derivatives	Codeine, Morphine
Phenothiazines	Prochlorperazine (Compazine), Promethazine (Phenergan)
Serotonin-reuptake inhibitors (SSRIs)	Fluoxetine (Prozac), Paroxetine (Paxil)
Tricyclic antidepressants	Amitriptyline (Elavil), Imipramine (Tofranil)
Individual Medications Associated with Hyponatremia	
Carbamazepine (Tegretol)	
Chlorpropamide (Diabinese)	
Clofibrate (Atromid-S)	
Cyclophosphamide (Cytoxan)	
Desmopressin (DDAVP; nasal or oral)	
Lamotrigine (Lamictal)	
Oxytocin (Pitocin)	
Vincristine (Oncovin)	

The Adequate Intake (AI) for Sodium

In 2019, the Food and Nutrition Board (FNB) of the National Academy of Medicine revised the Dietary Reference Intakes (DRIs) for sodium (20). The FNB did not find sufficient evidence to determine an Estimated Average Requirement (EAR) and derive a Recommended Dietary Allowance (RDA). Instead, they established an adequate intake (AI) for sodium (**Table 2**; 20). Considerations accounted for by the FNB for establishing an AI for sodium included that the available evidence was insufficient to identify adverse health effects associated with low dietary sodium intakes and that there was substantial evidence suggesting potential long-term health benefits associated with reducing habitual sodium intakes below 2,300 mg/day (see The Chronic Disease Risk Reduction Intake for sodium). The AI could not be derived from the average dietary intakes of apparently healthy people in the US since average intake levels are well above 2,300 mg/day (see Sources).

Table 2. Adequate Intake (AI) for Sodium and Sodium Chloride (Salt)

Life Stage	Age	Males and Females Sodium (mg/day)	Males and Females Salt (mg/day)*
Infants	0-6 months	110	280
Infants	7-12 months	370	930
Children	1-3 years	800	2,000
Children	4-8 years	1,000	2,500
Children	9-13 years	1,200	3,000
Adolescents	14-18 years	1,500	3,800
Adults	19 years and older	1,500	3,800
Pregnancy	14-50 years	1,500	3,800
Breast-feeding	14-50 years	1,500	3,800
*The AI for salt corresponds to the AI for sodium multiplied by 2.5.			

Sources

Most of the sodium and chloride in the diet comes from salt (21). Very little sodium occurs naturally in food. Instead, sodium is added to make certain foods shelf stable, and it is ubiquitously used in the US food supply such that all food groups contribute to sodium intake levels (21). It has been estimated that 75% of the salt intake in the US is derived from salt added during food processing or manufacturing, rather than from salt added at the table or during cooking (22). The lowest salt intakes are associated with diets that emphasize unprocessed foods, especially fruit, vegetables, and legumes. Combined data of the US National Health And Nutrition Examination Surveys (NHANES) 2007-2008 and 2009-2010 indicated average dietary sodium intakes of 3,100 mg/day in children (ages, 3-18 years), 3,800 mg/day in adults (ages, 19-50 years), and 3,300 mg/day in older adults (>50 years) (23). Usual intakes were estimated to be 4,400 mg/day and 3,100 mg/day in adult men and women (ages, 19-50 years), respectively. Overall, sodium intakes among males of all age groups were found to be 20%-45% higher than among females (23). These intakes are well above the sodium Chronic Disease Risk Reduction Intake (CDRR) of 2,300 mg/day (see The Chronic Disease Risk Reduction Intake for sodium).

Table 3 lists the sodium content (in milligrams [mg]) of some foods that are high in salt, and **Table 4** lists some foods that are relatively low in salt. Most sodium is consumed in the form of sodium chloride (salt). The salt content of foods can be calculated by multiplying the sodium content by 2.5.

Example: 2,000 mg (2 g) of sodium x 2.5 = 5,000 mg (5 g) of salt.

For more information on the sodium content of foods, search USDA's FoodData Central.

Table 3. Some Foods that are High in Sodium and Salt Content

Food	Serving	Sodium (mg)	Salt (mg)
Cereal, corn flakes	1 cup	182	445
Cereal, bran flakes	1 cup	216	540
Dill pickle	1 spear	283	707
Bread, whole-wheat	2 slices	291	727
Bread, white	2 slices	344	860
Hot dog (beef)	1	409	1,022
Cheese spread, pasteurized	1 ounce	416	1,040
Fish sandwich with tartar sauce and cheese	1 sandwich	582	1,455
Tomato juice, canned, with salt added	1 cup (8 fl. ounces)	615	1,537
Chicken noodle soup, canned	1 cup	789	1,972
Macaroni and cheese, box	1 cup	869	2,173
Corned beef hash	1 cup	972	2,430
Pretzels, salted	2 ounces (10 pretzels)	1,029	2,572
Ham, minced	3 ounces	1,059	2,647
Potato chips, salted	8 ounces (1 bag)	1,196	2,990
Sunflower seeds, dry roasted, with salt added	1 ounce	1,703	4,257

Table 4. Some Foods that are Relatively Low in Sodium and Salt Content

Food	Serving	Sodium (mg)	Salt (mg)
Olive oil	1 tablespoon	0	0
Orange juice, frozen	1 cup (8 fl. ounces)	0	0
Almonds, unsalted	¼ cup	0.3	0.8
Popcorn, air-popped, unsalted	1 cup	1	3
Pear	1 medium	2	5
Mango	1 fruit	4	10
Tomato	1 medium	6	15
Fruit cocktail, canned	1 cup	9	23
Brown rice	1 cup, cooked	10	25
Potato chips, unsalted	8 ounces (1 bag)	18	45
Tomato juice, canned, without salt added	1 cup (8 fl. ounces)	24	60
Carrot	1 medium	42	105

The daily value (DV) for sodium is less than 2,400 mg. The % DV included on the Nutrition Facts label of packaged foods and beverages is meant to help consumers make informed choices and consider the foods with low (≤5% DV per serving) rather than high (≥20% DV per serving) sodium content (24).

Safety

Toxicity

Excessive intakes of sodium chloride lead to an increase in extracellular fluid volume as water is pulled from cells to maintain normal sodium concentrations outside of cells. However, as long as water needs can be met, normally functioning kidneys can excrete the excess sodium and restore the system to normal (1). Ingestion of large amounts of salt may lead to nausea, vomiting, diarrhea, and abdominal cramps (25). Hypernatremia, defined as serum sodium concentrations ($[Na^+]$) >145 mM, is much less common than hyponatremia and rarely caused by excessive sodium intake (e.g., from the ingestion of large amounts of seawater or intravenous infusion of concentrated saline solution) (26). Hypernatremia generally develops from excess water loss (e.g., burns, respiratory infections, renal loss, osmotic diarrhea, hypothalamic disorders) or reduced water intake, frequently accompanied by an impaired thirst mechanism (6). Symptoms of hypernatremia with evidence of dehydration from excessive water loss may include dizziness or fainting, low blood pressure, and diminished urine production. Severe hypernatremia ($[Na^+]$ >158 mM) may result in altered mental status, lethargy, irritability, stupor, convulsions, and coma. Acute brain shrinkage can lead to intracranial and subarachnoid hemorrhage (26).

The Dietary Reference Intakes (DRIs) for sodium were recently revised by the Food and Nutrition Board of the National Academy of Medicine (20). Using a new expanded DRI model, the National Academy of Medicine did not find sufficient evidence of adverse toxicological effects of excessive sodium intake; therefore, they did not establish a tolerable upper intake level (UL) for sodium (20).

Health risks of excess dietary sodium

Hypertension

Normal blood pressure is defined by a systolic blood pressure below 120 mm Hg and a diastolic blood pressure below 80 mm Hg, often noted <120/80 mm Hg (27). Currently, about one-third of US adults have hypertension (blood pressure levels ≥140/90 mm Hg), and another one-third have elevated blood pressure (prehypertension, corresponding to levels ≥120/80 mm Hg and <140/90 mm Hg) that places them at risk for hypertension (28). Chronic hypertension damages the heart, blood vessels, and kidneys, thereby increasing the risk of heart disease and stroke, as well as hypertensive kidney disease. In a number of clinical studies, salt intake has been significantly correlated with left ventricular hypertrophy, an abnormal thickening of the heart muscle, which is associated with increased mortality from cardiovascular disease (29). Several lines of research, conducted over the last decades, have provided evidence of a relationship between sodium consumption and health outcomes. For instance, observational cohort studies, like the well-designed International Study of Salt and Blood Pressure (INTERSALT), have associated excess sodium intake with a progressive increase of blood pressure with age (30, 31). Further, a number of intervention studies, including the Trial of Nonpharmacologic Interventions in the Elderly (TONE), Trials Of Hypertension Prevention (TOHP), and Dietary Approaches to Stop Hypertension (DASH)-sodium, have demonstrated that dietary sodium reduction could effectively prevent or improve hypertension among population subgroups at elevated risk (see Blood pressure clinical trials).

Salt sensitivity: Blood pressure responses to short-term changes in sodium intake are heterogeneous. Indeed, some individuals have little-to-no change in blood pressure in response to sodium manipulation and are identified as "salt-resistant." In contrast, individuals who experience a greater change in blood pressure following dietary sodium manipulation are labeled "salt sensitive" (32, 33). Most of the protocols used in salt sensitivity studies involve extreme manipulations of sodium intake (sodium loading and sodium depletion) over a short timespan of a few days or up to one week. A typical controlled isocaloric intervention may include a two-phase, randomized, cross-over seven-day dietary sodium manipulation with a high-sodium diet (6.9 to 8.1 g/day) and a very-low-sodium diet (0.5 g/day). Salt resistance is often defined as a change of ≤5 mm Hg in 24-h mean arterial pressure (MAP) between a high-sodium diet and a low-sodium diet. Conversely, salt sensitivity is defined by changes of >5 mm Hg in MAP between high- and low-sodium diets (34).

About 26% of normotensive and 51% of hypertensive individuals are estimated to be salt sensitive (35). Salt sensitivity among normotensive subjects has been found to predict future hypertension (36, 37). Long-term prospective cohort studies also provided substantial evidence suggesting that sensitivity to salt may be an independent risk factor for cardiovascular disease (reviewed in 38). Salt sensitivity involves greater sodium reabsorption in the kidney proximal tubules and higher glomerular filtration rate (GFR) on a high-sodium diet than salt resistance. The rise in blood pressure is thought to compensate high sodium and fluid retention by triggering increased renal excretion. Conversely, salt resistance is associated with adequate excretion of excess sodium such that consumption of large amounts of sodium does not markedly increase blood pressure (1).

Earlier observations suggested that certain subgroups of the population, including African Americans, older individuals (>45 years), and hypertensive patients, tended to have greater average blood pressure responses to changes in sodium intake (38). Nevertheless, a recent meta-analysis of randomized controlled trials found marginal ethnic differences in blood pressure response to sodium reduction (for at least one week) compared to previously reported data (39). Research examining a genetic basis for salt sensitivity may eventually lead to better and reliable classification of individuals for salt sensitivity. Yet, at present, the analyses of common variations (known as polymorphisms) in the sequence of specific genes involved in sodium retention by the kidney failed to show consistent results (reviewed in 40). A recent meta-analysis of nine observational studies failed to show significant associations between specific gene polymorphisms in the renin-angiotensin-aldosterone system and blood pressure response to salt (41). Other polymorphisms in genes like those coding for G-protein coupled receptor kinase type 4 (GRK4), epithelial sodium channels (ENaC) and regulators, or α-adducin may favor sodium retention by the kidney, hence predisposing to blood pressure sensitivity to salt (reviewed in 40). Finally, in addition to genetic predispositions, factors like diet quality (e.g., the DASH diet) and body weight probably influence blood pressure sensitivity to salt (38).

Blood pressure clinical trials: Of particular importance are the results of long-term multicenter trials that are the most relevant to clinical and public health practice, i.e., TONE (42), TOHP (43), and DASH (Dietary Approaches to Stop Hypertension)-sodium. TONE showed that modest reduction in sodium intake by about 1.0 g/day (~2.5 g/day of salt) resulted in a better control of hypertension in older adults who initially were on blood pressure medication (42). TOHP-Phase II (the second of two hypertension prevention trials) showed that a similar level of sodium reduction significantly reduced systolic (but not diastolic) blood pressure by 1.2 mm Hg in overweight participants with prehypertension after three years and limited the onset of hypertension by 18% after four years compared to usual care (no dietary intervention) (43, 44). Adherence to the DASH diet, which emphasizes fruit, vegetables, whole grains, poultry, fish, nuts, and low-fat dairy products, was found to substantially lower systolic/diastolic blood pressures by 11.4/5.5 mm Hg in hypertensive and 3.5/2.1 mm Hg in normotensive people compared to a typical US diet (45). The DASH diet is also markedly higher in potassium and calcium, modestly higher in protein, and lower in total fat, saturated fat, cholesterol, red meat, sweets, and sugar-containing beverages than the typical US diet. The DASH-sodium trial compared the DASH diet to a typical US (control) diet at three levels of sodium intake: low (1.5 g/day, current AI), intermediate (2.3 g/day, recommended as an upper level by US dietary guidelines), and high (3.2 g/day, typical US intake) levels (46). At each level of sodium intake, systolic and diastolic blood pressures were systematically lower in (pre)hypertensive people (blood pressure >120/80 mm Hg) consuming the DASH diet compared to the control diet. Reduction of sodium intake also significantly reduced blood pressure in hypertensive consumers of either the DASH diet or the typical US diet. Yet, in prehypertensive participants, the blood pressure-lowering effect of sodium reduction was only significant in those consuming the typical US diet; sodium reduction failed to reduce blood pressure in all prehypertensive participants assigned to the DASH diet, with the exception of African Americans. Compared to the high-salt control diet, average blood pressure in (pre)hypertensive participants on the low-sodium DASH diet was decreased by 8.9/4.5 mm Hg. Results of the DASH trials support the idea that sodium reduction in the context of a healthful dietary pattern offers an effective approach to the prevention and treatment of hypertension (47).

A majority of randomized clinical trials have examined the effect of dietary sodium reduction on blood pressure in (pre)hypertensive rather than in normotensive (normal blood pressure) people. A recent meta-analysis assessed the results of modest sodium reduction from 22 trials in 990 participants with hypertension (blood pressure ≥140/90 mm Hg) and 12 trials in 2,240 participants without hypertension (blood pressure <140/90 mm Hg). A modest sodium reduction by 1.8 g/day (equivalent to 4.4 g/day of salt; based on 24-hour urinary sodium excretions) for at least four weeks decreased systolic and diastolic blood pressure by an average of 5.4/2.8 mm Hg in subjects with hypertension and 2.4/1.0 mm Hg in those without hypertension (48). Another pooled analysis of eight randomized controlled studies demonstrated a dose-response relationship between sodium reduction (by 1.8 to 3.2 g/day) and blood pressure in subjects with blood pressure over 130/80, but there was no such relationship in subjects whose blood pressure was below 130/80 (49).

The 2015-2020 Dietary Guidelines for Americans concurred with the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline to recommend that individuals who would benefit from blood pressure lowering, particularly prehypertensive and hypertensive adults, should follow the DASH eating pattern to lower sodium intakes (50). Recommendations include sodium intakes of no more than 2.4 g/day, further sodium intake reduction to 1.5 g/day for an even greater blood pressure-lowering effect, or a reduction is sodium intake of at least 1 g/day if sodium intakes of 1.5 g/day or 2.4 g/day cannot be achieved (50, 51).

More information about the DASH diet is available from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

Endothelial dysfunction

Early studies in animals and humans reported that high-salt intake was associated with pathological alterations in the structure and function of large elastic arteries, independent of changes in blood pressure (reviewed in 52). Endothelial dysfunction is considered to be an early step in the development of atherosclerosis. Alterations in the structure and function of the vascular endothelium that lines the inner surface of all blood vessels are associated with the loss of normal nitric oxide (NO)-mediated endothelium-dependent vasodilation. Endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities. The measurement of brachial artery flow-mediated dilation (FMD) is often used as a functional marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (53).

The link between sodium intake and cardiovascular disease has traditionally involved hypertension. Yet, recent investigations in salt-resistant normotensive individuals have reported that dietary sodium loading could impair endothelial function independent of changes in blood pressure (54, 55). A study using controlled dietary sodium conditions also demonstrated that a high-sodium diet (6.9 g/day for one week) reduced brachial artery FMD to the same extent in salt-sensitive and salt-resistant normotensive participants (56). On the other hand, a three-week dietary sodium intake of 3 g following a baseline intake of 2.4 g/day of sodium did not lower FMD in 36 untreated (pre)hypertensive adults with baseline FMD values significantly lower than those usually observed in healthy normotensive subjects (57). Circulating markers of endothelial function and low-grade inflammation were unchanged; only urinary sodium excretion and systolic blood pressure increased (57).

In healthy normotensive adults in whom FMD significantly decreased following a meal containing 1.5 g of sodium, potassium supplementation (1.5 g) could limit high sodium-induced FMD reduction in the postprandial state (58, 59). In a 12-week, randomized, cross-over study in 25 overweight/obese and normotensive subjects, a diet containing 2.3 g/day reduced FMD after two days and for six weeks, compared to a diet containing 3.5 g/day (60). In another randomized, cross-over, placebo-controlled trial, dietary sodium restriction (1.2 g/day vs. 3.5 g/day) for five weeks significantly lowered systolic (but not diastolic) blood pressure by 12 mm Hg and increased FMD by 68% in 17 (pre)hypertensive subjects (mean age, 62 years) (61). The improvements in both blood pressure and endothelial function suggest that sodium restriction has a strong potential for reducing CVD risk by preserving the vasculature.

Cardiovascular morbidity and mortality

A high dietary sodium intake is a risk factor for cardiovascular disease. A pooled analysis of 13 prospective cohort studies in 177,025 participants followed for 3 to 17 years found greater risks of cardiovascular disease (+17%) and stroke (+23%) with an average difference of 2 g of sodium (5 g of salt) between higher and lower daily consumption across the studies (62). Higher sodium intakes were also found to be associated with an increased risk of stroke (+24%) — but not with the risk of cardiovascular disease or coronary heart disease — in a more recent meta-analysis of 10 prospective cohort studies and randomized controlled trials (63).

A meta-analysis of randomized controlled studies examined the effect of dietary sodium reduction on cardiovascular events and mortality (64). Dietary interventions aiming at reducing sodium intake failed to demonstrate an effect on all-cause mortality in hypertensive and non-hypertensive individuals. Current evidence also fails to support a decrease in cardiovascular morbidity and mortality in patients with hypertension (64). Likewise, the Centers for Disease Control and Prevention (CDC)-sponsored 2013 report on *Sodium Intake in Populations* by the US Institute of Medicine (IOM; renamed the National Academy of Medicine) indicated that evidence was scarce and of poor quality to assess whether sodium intakes below 2.3 g/day may lower the risk of heart disease, stroke, and all-cause mortality in the general US population (65). In addition, the IOM committee found no evidence of benefits but some evidence of potential harm in reducing sodium intakes to 1.5 g/day-2.3 g/day in individuals with diabetes mellitus, kidney disease, or cardiovascular disease (65). However, in a recent review of the literature, the US Agency for Healthcare Research and Quality (AHRQ) identified low strength evidence to suggest that sodium reduction could decrease the risk of a composite measure of cardiovascular outcomes (seven trials) and the risk of combined cardiovascular morbidity and mortality (eight trials) (66).

Gastric cancer

In the evidence-based report, *Food, Nutrition, Physical Activity, and the Prevention of Cancer* (2007), the World Cancer Research Fund/American Institute for Cancer Research concluded that salt was a probable cause of stomach cancer (67). A recent meta-analysis of seven prospective cohort studies in nearly 270,000 participants showed a 68% greater risk of gastric cancer with the highest versus lowest salt intake level (68). Findings from observational studies, conducted mainly in Asian countries, also suggested an increased risk of gastric cancer with high intakes of salted foods, pickled foods, and processed meat products (68-70). Low intakes of fruit and vegetables, which are protective against gastric cancer, in populations with high intakes of salted foods might also contribute to increasing the risk of gastric cancer (69, 71).

Animal studies suggested that high concentrations of salt may damage the cells lining the stomach, potentially increasing the risk of bacterial infection by *Helicobacter pylori* (72, 73) and cancer-promoting genetic damage (74). The colonization by *H. pylori* is a recognized risk factor for gastric cancer. Case-control studies examining the potential interaction between salt intake and *H. pylori* infection in the risk of gastric cancer have provided mixed results (75-78). Although there is little evidence that salt itself is a carcinogen, high intakes of salted foods may increase the risk of gastric cancer in individuals infected with *H. pylori* or exposed to gastric carcinogens (67). Salty foods, like processed meat, cured meat, and salted fish, contain high levels of nitrosated compounds that may contribute to increasing the risk of gastric cancer (67).

Osteoporosis

Osteoporosis is a multifactorial skeletal disorder in which bone strength is compromised, resulting in an increased risk of fracture. Nutrition is one of many factors contributing to the development and progression of osteoporosis. Dietary sodium is a major determinant of urinary calcium loss (79). High-sodium intake results in increased loss of calcium in the urine, possibly due to competition between sodium and calcium for reabsorption in the kidneys or by an effect of sodium on parathyroid hormone (PTH) secretion (see the article on Calcium). Every 1-g increment in sodium (2.5 g of salt) excreted by the kidneys has been found to draw about 26.3 mg of calcium into the urine (79). A study conducted in adolescent girls reported that a high-salt diet had a greater effect on urinary sodium and calcium excretion in White compared to Black girls, suggesting differences among ethnic groups (80). In adult women, each extra gram of sodium consumed per day is projected to produce an additional rate of bone loss of 1% per year if all of the calcium loss comes from the skeleton.

A number of cross-sectional and intervention studies have suggested that high-sodium intakes are deleterious to bone health, especially in older women (81). In particular, high-sodium intake in conjunction with low-calcium intake may be especially detrimental to bone health (82-84). A two-year longitudinal study in postmenopausal women found increased urinary sodium excretion (an indicator of increased sodium intake) to be associated with decreased bone mineral density (BMD) at the hip (85). Linear regression analysis estimated that BMD could be maintained by reducing sodium intake to a level of 2.3 g/day and by increasing calcium intake to 1.2 g/day. A second longitudinal study in postmenopausal women found that habitual sodium intake of approximately 3 g/day was not detrimental to BMD over three years of follow-up (86). Notably, the average calcium intake in this study population was 1.3 to 1.5 g/day — slightly above the RDA for calcium in women over 50 years. Another study in 40 postmenopausal women found that adherence to a low-sodium diet (2 g/day) for six months was associated with significant reductions in sodium excretion, calcium excretion, and aminoterminal propeptide of type I collagen (a biomarker of bone resorption). Yet, these associations were only observed in women with elevated baseline urinary sodium excretions (87). Finally, in a randomized, placebo-controlled study in 60 postmenopausal women, potassium citrate supplementation prevented an increase in calcium excretion induced by the consumption of a high-sodium diet (≥5 g/day of sodium) for four weeks (88).

Kidney stones

Most kidney stones are composed of calcium oxalate or calcium phosphate. Subjects with an abnormally high level of calcium in the urine (hypercalciuria) are at higher risk of developing kidney stones (a process called nephrolithiasis) (89). A large prospective cohort study that followed more than 90,000 women over a 12-year period found that women with a sodium intake averaging 4.9 g/day (12.6 g/day of salt) had a 30% higher risk of developing symptomatic kidney stones than women whose sodium intake averaged 1.5 g/day (3.8 g/day of salt) (90). Because urinary calcium excretion is increased by high sodium intakes (79), dietary sodium restriction may reduce the risk of stone formation, especially in patients with a history of kidney stones, by limiting calcium excretion (91). A five-year, randomized intervention study that enrolled 120 men with idiopathic hypercalciuria (mean age, 45 years) reported that those assigned to a normal-to-high calcium (1.2 g/day) and low-sodium diet (1.2 g/day) had a 49% reduced risk of kidney stone recurrence compared to those on a low-calcium diet (~0.4 g/day) (92).

The Chronic Disease Risk Reduction Intake

In 2004, the Food and Nutrition Board (FNB) of the National Academy of Medicine (formerly, the Institute of Medicine [IOM]) established a tolerable upper intake level (UL) of 2.3 g/day sodium (5.8 g/day of salt) for adults based on the adverse effects of high sodium intakes on blood pressure, a major risk factor for cardiovascular and kidney diseases (93). The 2015-2020 Dietary Guidelines for Americans report also recognizes that excess sodium consumption poses potential health risks and emphasizes the reduction of sodium intake in the context of a healthful dietary pattern, following the UL set by the IOM panel (50).

In a 2019 update of the Dietary Reference Intakes (DRIs) for sodium, the National Academy of Medicine made use of a new expanded DRI model (20). As a consequence, only evidence of a toxicological risk associated with excessive sodium intakes was considered to establish a UL for sodium (20), whereas previously the UL for sodium was based on evidence of any type of adverse effects (93). In addition, the evidence of the relationship between sodium intake levels, blood pressure, and cardiovascular disease — considered toward establishing a UL in the previous report — has now been reviewed to establish a new DRI category, namely the Chronic Disease Risk Reduction Intake (CDRR) for sodium (20).

Using the expanded DRI model, the National Academy of Medicine did not find sufficient evidence of adverse toxicological effects to establish a UL for sodium (20).

In contrast, substantial evidence from trials showing a lowering of the risks of hypertension and cardiovascular disease with reduction of sodium intakes was used to set a CDRR for sodium in apparently healthy adults at 2,300 mg/day (20). The CDRR for healthy adults means that a lowering of usual sodium intakes to at least 2,300 mg/day from higher levels is expected to reduce the risk of chronic disease.

The CDRR values for other ages/life stages have been extrapolated from the CDRR value set for adults using estimated energy requirements; these CDRR-based recommendations for each age/life stage are presented in **Table 5**.

Table 5. Sodium Chronic Disease Risk Reduction Intake (CDRR)-based Recommendations

Age Group	Recommendation
Infants 0-12 months	Not Determined
Children 1-3 years	Reduce intakes if above 1,200 mg/day*
Children 4-8 years	Reduce intakes if above 1,500 mg/day*
Children 9-13 years	Reduce intakes if above 1,800 mg/day*
Adolescents 14-18 years	Reduce intakes if above 2,300 mg/day*
Adults 19 years and older	Reduce intakes if above 2,300 mg/day
*Extrapolated from the adult CDRR using estimated energy requirements.	

Of note, in its 2013 report on *Sodium Intake in Populations*, the FNB committee considered that recommendations to population subgroups, including those who are most sensitive to the blood pressure effects of sodium, like older people (≥51 years), African Americans, and individuals with hypertension, diabetes mellitus, or chronic kidney disease, should be similar to those for the general US population (65). The IOM committee found no supportive evidence to recommend that these subgroups lower their sodium intake to 1.5 g/day or below (65). In contrast, the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on Lifestyle Management to Reduce Cardiovascular Risk advises adults with (pre)hypertension to consume no more than 2.4 g/day of sodium, further reduce sodium intake to 1.5 g/day for an even greater blood pressure-lowering effect, or reduce their daily intake by at least 1 g if sodium intakes of 1.5 g/day or 2.4 g/day cannot be achieved (51).

Finally, the 2010 IOM report on *Strategies to Reduce Sodium Intake in the United States* suggested that the US Food and Drug Administration (FDA) revisit the Generally Recognized As Safe (GRAS) status of salt added to processed food, restaurant food, and food additives, in order to reduce the salt content in the food supply and assist in achieving sodium intakes consistent with US Dietary Guidelines and IOM recommendations (21). These recommendations are currently being reviewed by the FDA (22).

Drug interactions

Taking sodium bicarbonate orally may reduce the efficacy of the antibiotic cefpodoxime and the antidiabetic drug chlorpropamide by limiting drug absorption or increasing drug urinary excretion. Intravenous administration of sodium bicarbonate may also reduce the effects of aspirin and the nasal decongestant pseudoephedrine. Excessive intake of sodium bicarbonate may increase the risk of hypokalemia (abnormally low blood potassium concentration) in patients taking potassium-depleting drugs like diuretics (e.g., hydrochlorothiazide, furosemide, or bumetanide), the anti-gout agent colchicine, and calcium- or magnesium-containing antacids (94).

Linus Pauling Institute Recommendation

There is strong and consistent evidence that diets relatively low in sodium (2.3 g/day or less) and high in potassium are associated with decreased risk of high blood pressure and the related risks of cardiovascular and kidney diseases. Moreover, the DASH trial demonstrated that a diet emphasizing fruit, vegetables, whole grains, nuts, and low-fat dairy products substantially lowered blood pressure, an effect that was enhanced by reducing salt intake to 2.3 g/day of sodium (5.8 g/day of salt). The Linus Pauling Institute recommends a diet that is rich in fruit and vegetables (at least 9 servings/day) and limits processed foods that are high in salt.

Older adults (>50 years)

Since sensitivity to the blood pressure-raising effect of salt increases with age, sodium reduction in the context of a healthful dietary pattern may especially benefit older adults, who are at increased risk of high blood pressure, cardiovascular disease, and kidney disease.

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Zinc

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Summary

- Zinc is a nutritionally essential mineral needed for catalytic, structural, and regulatory functions in the body. *(More information)*
- Severe zinc deficiency is rare and caused by an inherited condition called acrodermatitis enteropathica. Acquired zinc deficiency is primarily due to malabsorption syndromes and chronic alcoholism. *(More information)*
- Dietary zinc deficiency is quite common in the developing world, affecting an estimated 2 billion people. Consumption of diets high in phytate and lacking foods from animal origin drive zinc deficiency in these populations. *(More information)*
- The recommended dietary allowance (RDA) for adult men and women is 11 mg/day and 8 mg/day of zinc, respectively. *(More information)*
- Long-term consumption of zinc in excess of the tolerable upper intake level (UL; 40 mg/day for adults) can result in copper deficiency. *(More information)*
- Dietary zinc deficiency has been associated with impaired growth and development in children, pregnancy complications, and immune dysfunction with increased susceptibility to infections. *(More information)*
- Supplementation with doses of zinc in excess of the UL is effective to reduce the duration of common cold symptoms. The use of zinc at daily doses of 50 to 180 mg for one to two weeks has not resulted in serious side effects. *(More information)*
- Current evidence suggests that supplemental zinc may be useful in the management of chronic conditions, such as age-related macular degeneration, diabetes mellitus, Wilson's disease, and HIV/AIDS. *(More information)*
- Zinc bioavailability is relatively high in meat, eggs, and seafood; zinc is less bioavailable from whole grains and legumes due to their high content in phytate that inhibits zinc absorption. *(More information)*

Zinc is an essential trace element for all forms of life. Clinical zinc deficiency in humans was first described in 1961, when the consumption of diets with low zinc bioavailability due to high phytate content (see Food sources) was associated with "adolescent nutritional dwarfism" in the Middle East (1). Since then, zinc insufficiency has been recognized by a number of experts as an important public health issue, especially in low-resource countries (2, 3).

Function

Numerous aspects of cellular metabolism are zinc-dependent. Zinc plays important roles in growth and development, immune function, neurotransmission, vision, reproduction, and intestinal ion transport (4). Using data mining approaches, it has been estimated that over 3,000 proteins in humans have functional zinc-binding sites (5). At the cellular level, the function of zinc can be divided into three categories: (1) catalytic, (2) structural, and (3) regulatory (6).

Catalytic role

Over 50 different enzymes depend on zinc for their ability to catalyze vital chemical reactions (7). Zinc-dependent enzymes can be found in all six classes of enzymes (8), as defined by the International Union of Biochemistry and Molecular Biology (9). During enzymatic reactions, zinc may have either a direct catalytic role or a structural role (i.e., stabilizing the structure of catalytic enzymes; see below).

Structural role

Zinc plays an essential role in the folding of some proteins. A finger-like structure, known as a zinc finger motif, stabilizes the structure several proteins. Examples of zinc finger proteins include the superfamily of nuclear receptors that bind and respond to steroids and other molecules, such as estrogens, thyroid hormones, vitamin D, and vitamin A (10). Zinc finger motifs in the structure of nuclear receptors allow them to bind to DNA and act as transcription factors to regulate gene expression (see Regulatory role). Zinc finger motifs are also involved in interactions of proteins with other proteins, ribonucleotides, and lipids (6). Removal of zinc from zinc-containing proteins results in protein misfolding and loss of function.

Metallothioneins are examples of proteins with a zinc-binding motif. Metallothioneins are small metal-binding cysteine-rich proteins with a high affinity for zinc. They work in concert with zinc transporters, regulating free zinc concentrations in the cytosol (11). Metallothioneins are also involved in the regulation of metal ion homeostasis, cellular defense against oxidative stress, and detoxification of heavy metals (11, 12).

The antioxidant enzyme, copper-zinc superoxide dismutase 1 (SOD 1), is made of two identical dimers, each including an active site with a catalytic copper ion and a structural zinc ion. Demetalation of SOD1 has been implicated in the formation of amyloid aggregates in some forms of inherited amyotrophic lateral sclerosis (ALS) — a motor neuron disease leading to muscle atrophy and paralysis (13).

Regulatory role

Zinc finger proteins have been found to regulate gene expression by acting as transcription factors (see above). Zinc also plays a role in cell signaling via the metal-response element (MRE)-binding transcription factor 1 (MTF1); MTF1 has a zinc finger domain that allows its binding to MRE sequences in the promoter of target genes and the subsequent expression of zinc-responsive genes (6). Zinc may also have a direct regulatory function, modulating the activity of cell-signaling enzymes and transcription factors (6). Extracellular zinc can also stimulate a zinc-sensing receptor that triggers the release of intracellular calcium, a second messenger in signaling pathways (14). Zinc has been found to influence hormone release (see Type 2 diabetes mellitus) (15) and nerve impulse transmission (16).

Nutrient interactions

Copper

Taking large quantities of zinc (50 mg/day or more) over a period of weeks can interfere with copper bioavailability. High intake of zinc induces the intestinal synthesis of a copper-binding protein called metallothionein (see the article on Copper). Metallothionein traps copper within intestinal cells and prevents its systemic absorption (see Wilson's disease). More typical intakes of zinc do not affect copper absorption, and high copper intakes do not affect zinc absorption (17).

Iron

Iron and zinc compete for absorptive pathways (18). Supplemental (38-65 mg/day of elemental iron) but not dietary levels of iron may decrease zinc absorption (18, 19). This interaction is of concern in the management of iron supplementation during pregnancy and lactation and has led some experts to recommend zinc supplementation for pregnant and lactating women taking iron supplements (20, 21). Food fortification with iron has not been shown to negatively affect zinc absorption (22). In a placebo-controlled study, supplementation with zinc (10 mg/day) for three months in children aged eight to nine years significantly decreased serum iron concentrations, yet not to the extent of causing anemia (23). Additional randomized controlled studies have reported a worsening of nutritional iron status with chronic zinc supplementation (24, 25).

Calcium

High levels of dietary calcium impair zinc absorption in animals, but it is uncertain whether this occur in humans (17). One study showed that increasing the calcium intake of postmenopausal women by 890 mg/day in the form of milk or calcium phosphate (total calcium intake, 1,360 mg/day) reduced zinc absorption and zinc balance in postmenopausal women (26). However, another study found that increasing the calcium intake of adolescent girls by 1,000 mg/day in the form of calcium citrate malate (total calcium intake, 1,667 mg/day) did not affect zinc absorption or balance (27). Calcium in combination with phytate might affect zinc absorption, which would be particularly relevant to individuals who very frequently consume tortillas made with lime (i.e., calcium oxide). A study in 10 healthy women (age range, 21-47 years) found that high intake of dietary calcium (~1,800 mg/day) did not impair zinc absorption regardless of the phytate content of the diet (28). For more information on phytate, see Food sources.

Folate

The bioavailability of dietary folate (vitamin B_9) is increased by the action of a zinc-dependent enzyme. Accordingly, some studies found low zinc intake decreased folate absorption. It was also suggested that supplementation with folic acid — the synthetic form of folate — might impair zinc utilization in individuals with marginal zinc status (17, 29). However, one study reported that supplementation with a relatively high dose of folic acid (800 μg/day) for 25 days did not alter zinc absorption or status in a group of students being fed a low-zinc diet (3.5 mg/day) (30).

Vitamin A

Zinc and vitamin A interact in several ways. Zinc is a component of retinol-binding protein, a protein necessary for transporting vitamin A in the blood. Zinc is also required for the enzyme that converts retinol (vitamin A) to retinal. This latter form of vitamin A is necessary for the synthesis of rhodopsin, a protein in the eye that absorbs light and thus is involved in dark adaptation. Zinc deficiency has been associated with a decreased release of vitamin A from the liver, which may contribute to symptoms of night blindness that are seen with zinc deficiency (31, 32).

Deficiency

Inherited zinc deficiency

Much of what is known about severe zinc deficiency was derived from the study of individuals born with acrodermatitis enteropathica, a genetic disorder resulting from the impaired uptake and transport of zinc (33). The symptoms of severe zinc deficiency include the slowing or cessation of growth and development, delayed sexual maturation, characteristic skin rashes, chronic and severe diarrhea, immune system deficiencies, impaired wound healing, diminished appetite, impaired taste sensation, night blindness, swelling and clouding of the cornea, and behavioral disturbances. Before the cause of acrodermatitis enteropathica was known, patients typically died in infancy. Oral zinc therapy results in the complete remission of symptoms, though it must be maintained indefinitely in individuals with the genetic disorder (33, 34).

Acquired zinc deficiency

It is now recognized that milder zinc deficiency contributes to a number of health problems, especially common in children who live in low-resource countries. An estimated 2 billion people worldwide are affected by dietary zinc deficiency (3). The lack of a sensitive and specific indicator of marginal zinc deficiency hinders the scientific study of its health implications (8). However, controlled trials of moderate zinc supplementation have demonstrated that marginal zinc deficiency contributes to impaired physical and neuropsychological development and increased susceptibility to life-threatening infections in young children (34). In fact, zinc deficiency has been estimated to cause more than 450,000 deaths annually in children under five years of age, comprising 4.4% of global childhood deaths (35). For a more detailed discussion of the relationship of zinc deficiency to health problems, see the section on Disease Prevention.

In industrialized countries, dietary zinc deficiency is unlikely to cause severe zinc deficiency in individuals without a genetic disorder, zinc malabsorption or conditions of increased zinc loss, such as severe burns or prolonged diarrhea. Severe zinc deficiency has also been reported in individuals undergoing total parenteral nutrition without zinc, in those who abuse alcohol, and in those who are taking certain medications like penicillamine (see Drug interactions) (36).

Individuals at risk of zinc deficiency (6, 36-38):

- Premature and low-birth-weight infants
- Older breast-fed infants and toddlers with inadequate intake of zinc-rich complementary foods
- Children and adolescents
- Pregnant and lactating (breast-feeding) women, especially adolescents
- Patients receiving total parenteral nutrition (intravenous feedings)
- Malnourished individuals, including those with protein-energy malnutrition and anorexia nervosa
- Individuals with severe or persistent diarrhea
- Individuals with malabsorption syndromes, including celiac disease and short bowel syndrome
- Individuals with inflammatory bowel disease, including Crohn's disease and ulcerative colitis
- Alcoholics and those with alcoholic liver disease who have increased urinary zinc excretion and low liver zinc levels
- Individuals with chronic renal disease
- Individuals with sickle cell anemia
- Individuals who use medications that decrease intestinal zinc absorption, increase zinc excretion, or impair zinc utilization (see Drug interactions)
- Older adults (65 years and older)
- Vegetarians: The requirement for dietary zinc may be as much as 50% greater for vegetarians whose major food staples are grains and legumes, because high levels of phytate in these foods reduce zinc absorption (see Food sources) (29).

Biomarkers of zinc status

Currently, there is not a sensitive and specific biomarker to detect zinc deficiency in humans. Low plasma or serum zinc concentrations are typically used as indicators of zinc status in populations and in intervention studies, but they have a number of limitations, including lack of sensitivity to detect marginal zinc deficiency, diurnal variations, and confounding by inflammation, stress, and hormones (38, 39).

The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for zinc is listed by gender and age group in **Table 1**. Infants, children, adolescents, and pregnant and lactating women are at increased risk of zinc deficiency. Since a sensitive indicator of zinc nutritional status is not readily available, the RDA for zinc is based on a number of different indicators of zinc nutritional status and represents the daily intake likely to prevent deficiency in nearly all individuals in a specific age and gender group (29).

Table 1. The Recommended Dietary Allowance (RDA) for Zinc

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	3	3
Children	1-3 years	3	3
Children	4-8 years	5	5
Children	9-13 years	8	8
Adolescents	14-18 years	11	9
Adults	19 years and older	11	8
Pregnancy	18 years and younger	-	12
Pregnancy	19 years and older	-	11
Breast-feeding	18 years and younger	-	13
Breast-feeding	19 years and older	-	12

Prevention of Diseases or Conditions Related to Zinc Deficiency

Pregnancy complications and adverse pregnancy outcomes

Estimates based on national food supply indicate that dietary zinc intake is likely inadequate in most low- and middle-income countries, especially those in Sub-Saharan Africa and South Asia (40). Inadequate zinc status during pregnancy interferes with fetal development, and preterm neonates from zinc-deficient mothers suffer from growth retardation and dermatitis and are at risk of infections, necrotizing enterocolitis, chronic lung disease, and retinopathy of prematurity (4). Maternal zinc deficiency has also been associated with a number of pregnancy complications and poor outcomes. A recent case-control study conducted in an Iranian hospital reported higher odds of congenital malformations in newborns of mothers with low serum zinc concentrations during the last month of pregnancy (41). A 2016 review of 64 observational studies found an inverse relationship between maternal zinc status and the severity of preeclampsia, as well as between maternal zinc intake and the risk of low-birth-weight newborns (42). There were no apparent associations between maternal zinc status and the risk of gestational diabetes mellitus and preterm birth. However, the conclusions of this analysis were limited by the fact that most observational studies were conducted in women from populations not at risk for zinc deficiency (42).

To date, available evidence from maternal zinc intervention trials conducted worldwide does not support the recommendation of routine zinc supplementation during pregnancy. A 2015 systematic review and meta-analysis of 21 randomized controlled trials in over 17,000 women and their babies found a 14% reduction in premature deliveries with zinc supplementation during pregnancy, mainly in low-income women (43). This analysis, however, did not find zinc supplementation to benefit other indicators of maternal or infant health, including stillbirth or neonatal death, low birth weight, small-for-gestational age, and pregnancy-induced hypertension. There was also no effect of supplemental zinc on postpartum hemorrhage, maternal infections, congenital malformations, and child development outcomes (43). A recent review of 17 trials (of which 15 were conducted in low- and middle-income countries) found that maternal supplementation with multiple micronutrients (including, among others, zinc, iron, and folic acid) reduced the risk of low-birth-weight newborns and small-for-gestational age infants when compared to supplemental iron with or without folic acid (44). While multiple micronutrient supplementation would likely benefit pregnant women with coexisting micronutrient deficiencies in low- and middle-income countries, there is no evidence to recommend zinc supplementation in isolation in pregnant women from any settings (43, 45).

Impaired growth and development

Growth retardation

Significant delays in linear growth and weight gain, known as growth retardation or failure to thrive, are common features of mild zinc deficiency in children. In the 1970s and 1980s, several randomized, placebo-controlled studies of zinc supplementation in young children with significant growth delays were conducted in Denver, Colorado. Modest zinc supplementation (5.7 mg/day) resulted in increased growth rates compared to placebo (46). Several meta-analyses of growth data from zinc intervention trials have confirmed the widespread occurrence of growth-limiting zinc deficiency in young children, especially in low- and middle-income countries (47-49). A 2018 systematic review and meta-analysis identified 54 trials that examined the impact of zinc supplementation during infancy (on average, 7.6 mg/day for 30.9 weeks) or childhood (on average, 8.5 mg/day for 38.9 weeks) on child anthropometric measurements (50). There was evidence of a positive effect of supplemental zinc on children's height, weight, and weight-for-age Z score (WAZ), but neither on height-for-age Z score (HAZ) or weight-for-height Z score (WHZ). In addition, zinc supplementation did not reduce the risks of underweight (WAZ<-2 standard deviation [SD]), wasting (WHZ<-2 SD), or stunting (HAZ<-2 SD) in children (50). Although the exact mechanisms for the growth-limiting effect of zinc deficiency are not known, research indicates that zinc availability affects cell-signaling systems that coordinate the response to the growth-regulating hormone, insulin-like growth factor-1 (IGF-1) (51).

Delayed mental and psychomotor development in young children

Adequate nutrition in essential for brain growth and development, especially during the first 1,000 days of life — a critical period of development for all organs and systems spanning from conception to 24 months of age (52). Animal studies have established that zinc deficiency in early life interferes with normal brain development and cognitive functions (reviewed in 53). Data on the effect of zinc supplementation during pregnancy on infants' neurologic and psychomotor outcomes is very limited. In a randomized, placebo-controlled trial in African-American women, daily maternal supplementation with 25 mg of zinc from about 19 weeks' gestation had no effect on neurologic development test scores in their children at five years of age (54).

Several studies have reported on the effect of postnatal zinc supplementation on mental and motor development. Two early randomized controlled trials, one conducted in India and the other in Guatemala, suggested that postnatal supplementation with 10 mg/day of zinc resulted in toddlers being more vigorous (55) and functionally active (56). In one trial conducted in Brazilian newborns from low-income families and weighing between 1,500 g and 2,499 g at birth, neither zinc supplementation for eight weeks with 1 mg/day or 5 mg/day improved mental and psychomotor development at 6 or 12 months of age compared to a placebo and assessed using the Bayley Scales of Infant Development (BSID) for Mental Development Index (MDI) and Psychomotor Development Index (PDI) (57). Additionally, a randomized, placebo-controlled, double-blind trial in Chilean newborns (birth weights >2,300 g) from low-income families reported no effect of zinc supplementation (5 mg/day) on mental and psychomotor development indices at 6 and 12 months (58). Two other trials found that supplemental zinc failed to improve MDI or PDI at 12 months of age when zinc (10 mg/day) was given to six-month-old infants for six months (59) or at the end of the intervention in toddlers aged 12-18 months when zinc (30 mg/day) was given for four months (60). A 2012 Cochrane review of eight clinical trials found no evidence that postnatal zinc supplementation improves mental or motor development of infants and children from populations with presumably inadequate zinc status (61).

Impaired immune system function

Adequate zinc intake is essential in maintaining the integrity of the immune system (62), specifically for normal development and function of cells that mediate both innate (neutrophils, macrophages, and natural killer cells) and adaptive (B-lymphocytes and T-lymphocytes) immune responses (63). Because pathogens also require zinc to thrive and invade, a well-established antimicrobial defense mechanism in the body sequesters free zinc away from microbes (64). Another opposite mechanism consists in intoxicating intracellular microbes within macrophages with excess zinc (65). Through weakening innate and adaptive immune responses, zinc deficiency diminishes the capacity of the body to combat pathogens (63, 64). As a consequence, zinc-deficient individuals experience an increased susceptibility to a variety of infectious agents (66).

Increased susceptibility to infectious disease in children

Diarrhea: Zinc promotes mucosal resistance to infections by supporting the activity of immune cells and the production of antibodies against invading pathogens (63, 64, 67). Therefore, a deficiency in zinc increases the susceptibility to intestinal infections and constitutes a major contributor to diarrheal diseases in children (66). In turn, persistent diarrhea contributes to zinc deficiency and malnutrition (66). Research indicates that zinc deficiency may also potentiate the effects of toxins produced by diarrhea-causing bacteria like *E. coli* (68). It is estimated that diarrheal diseases are responsible for the deaths of about 500,000 children under five years of age annually in low- and middle-income countries (69). Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhea and to increase survival in a number of randomized controlled trials (70). A 2016 meta-analysis of randomized controlled trials found that zinc supplementation reduced the duration of acute diarrhea by one day in children aged >6 months who presented signs of malnutrition (5 trials; 419 children) (71). However, there was little evidence to suggest that zinc could be as efficacious to reduce the duration of acute diarrheal episodes in children aged <6 months and in well-nourished children aged >6 months. Zinc supplementation also reduced the duration of persistent diarrhea in children by more than half a day (5 trials; 529 children) (71).

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) currently recommend supplementing young children with 10 to 20 mg/day of zinc as part of the treatment for acute diarrheal episodes and to prevent further episodes in the two to three months following zinc supplementation (72).

Pneumonia: Pneumonia — caused by lower respiratory tract viral or bacterial infections (LRTIs) — accounts for nearly 1 million deaths among children annually, primarily in low-and middle-income countries (69). Vaccinations against *Haemophilus influenzae* type B, pneumococcus, pertussis (whooping cough), and measles can help prevent pneumonia (73). According to a 2009 WHO report on disease risk factors, zinc deficiency may be responsible for 13% of all LRTI cases, primarily pneumonia and flu cases, in children younger than 5 years (74). Accordingly, a 2016 meta-analysis of six trials found that zinc supplementation in children under 5 years old reduced the risk of pneumonia by 13% (75). However, it remains unclear whether supplemental zinc, in conjunction with antibiotic therapy, is beneficial in the treatment of pneumonia. A recent randomized, placebo-controlled trial conducted in Gambian children who were not zinc deficient failed to show any benefit of zinc supplementation (10 mg/day or 20 mg/day [depending on child's age] for 7 days) given alongside antibiotics in the treatment of severe pneumonia (76). A 2018 meta-analysis of five trials (1,822 participants) found no improvement when zinc was used as an adjunct to antibiotic treatment in children with pneumonia (77). There was, however, evidence that supplemental zinc reduced the risk of pneumonia-related mortality (3 trials; 1,318 participants) (77).

Malaria: Early studies have indicated that zinc supplementation may reduce the incidence of clinical attacks of malaria in children (78). A placebo-controlled trial in preschool-aged children in Papua New Guinea found that zinc supplementation reduced the frequency of health center attendance due to *Plasmodium falciparum* malaria by 38% (79). Additionally, the number of malaria episodes accompanied by high circulating parasite concentrations was reduced by 68%, suggesting that zinc supplementation may be of benefit in preventing more severe episodes of malaria. However, a six-month trial in more than 700 West African children did not find any difference in the frequency or severity of malaria episodes between children supplemented with zinc and those given a placebo (80). Another randomized controlled trial reported that zinc supplementation did not benefit preschool-aged children with acute, uncomplicated malaria (81). There is also little evidence to suggest that zinc supplementation could reduce the risk of malaria-related mortality in children (82). At present, there is not enough evidence to suggest a prophylactic and/or therapeutic role for supplemental zinc in the management of childhood malaria (48). A recent randomized, placebo-controlled trial did not provide clear-cut evidence of a protective effect of zinc (25 mg/day) administered to Tanzanian women during their first gestational trimester until delivery on the risk of placental malaria infection (83).

Age-related decline in immune function

Inadequate zinc status in elderly subjects is not uncommon and is thought to exacerbate the age-related decline in immune function (84). In one study, low serum zinc concentrations in nursing home residents were associated with higher risks of pneumonia and pneumonia-related and all-cause mortality (85). Trials examining the effects of zinc supplementation on immune function in middle-aged and elderly adults have given mixed results (reviewed in 86). Some studies showed mixed or no effects of zinc supplementation on parameters of immune function (87-89). However, zinc supplementation was found to have a positive impact on certain aspects of immune function that are affected by zinc deficiency, such as the decline in T-cell (a type of lymphocyte) function (90). For example, a randomized, placebo-controlled study in adults over 65 years of age found that zinc supplementation (25 mg/day) for three months increased blood concentrations of helper T-cells and cytotoxic T-cells (91). Additionally, a randomized, double-blind, placebo-controlled trial in 101 older adults (aged 50-70 years) with normal blood zinc concentrations showed that zinc supplementation at 15 mg/day for six months improved the helper T-cells/cytotoxic T-cells ratio, which tends to decline with age and is a predictor of survival (92). However, the study also suggested that a dose of 30 mg/day of zinc might reduce the number of B-lymphocytes, which play a central role in humoral immunity. Further, zinc supplementation had no effect on various immune parameters, including markers of inflammation, measures of granulocyte and monocyte phagocytic capacity, or cytokine production by activated monocytes (92).

A more recent trial examined the effect of daily supplementation with a multiple micronutrients, including 5 mg or 30 mg of zinc for three months, on zinc status and markers of immune function in institutionalized elderly participants (mean age, >80 years) with low serum zinc concentrations (93). Zinc status was improved with the 30 mg/day dose — but not with 5 mg/day — yet the most zinc-deficient individuals failed to achieve normal serum zinc concentrations within the intervention period. The number of circulating T-cells was also significantly increased in those who took the micronutrient supplement with the higher versus low dose of zinc (93).

More research is warranted before zinc supplementation could be recommended to older adults, especially those with no symptoms of declining immunity. Nonetheless, the high prevalence of zinc deficiency among institutionalized elderly adults should be addressed and would likely improve the performance of their immune systems (86).

Type 2 diabetes mellitus

There is a close relationship between zinc and insulin action. Specifically, in pancreatic β-cells, zinc is involved in insulin synthesis and storage in secretory vesicles. Zinc is released with the hormone when blood glucose concentrations increase (15). Zinc is also understood to stimulate glucose uptake and metabolism by insulin-sensitive tissues through triggering the intracellular insulin signaling pathway (94). Single-nucleotide polymorphisms (SNPs) in the *SLC30A8* (solute carrier family 30 member 8) gene, coding for a zinc transporter that co-localizes with insulin in β-cells, have been associated with higher risks of type 1 and type 2 diabetes mellitus (95), though the risk for type 2 diabetes mellitus was found to be reduced with rare protein-truncating variants of the gene (96). The first prospective cohort study to examine the risk of type 2 diabetes in relation to zinc intakes — the Nurses' Health Study (NHS) — followed 82,297 US registered female nurses for 24 years. The data analysis showed an 8% lower risk of type 2 diabetes with the highest versus lowest intake of dietary zinc (median values, 11.8 mg/day versus 4.9 mg/day) (97). This finding was consistent with the result of the Australian Longitudinal Study on Women's Health (ALSWH) that enrolled 8,921 women for six years and showed a 50% lower risk of diabetes with the highest versus lowest intake of energy-adjusted dietary zinc (98). Both NHS and ALSWH studies also reported a reduced risk of diabetes with higher versus lower zinc-to-heme iron ratios in the diet (97, 98), although the significance is unclear as nonheme iron, rather than heme iron, is known to interfere with dietary zinc absorption (see Nutrient interactions). Heme iron may be an indicator of red meat consumption, which has been positively associated with the risk of type 2 diabetes (99). However, two other prospective cohort studies — the Multi-Ethnic Study of Atherosclerosis (MESA; 4,982 participants) and the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study (232,007 participants) — failed to find evidence for an association between zinc intake and risk of type 2 diabetes (100, 101). Another recent prospective cohort study, the Malmo Diet and Cancer Study in 26,132 middle-aged Swedish participants followed for 19 years, found an increased risk of diabetes with higher dietary zinc intakes yet a lower risk of diabetes in zinc supplement users (versus non-users) and in those with a higher zinc-to-iron intake ratio (102). The authors reported a stronger inverse association between zinc-to-iron intake ratio and risk of diabetes among obese participants carrying a specific *SLC30A8* genotype (102).

The results of a few short-term intervention studies suggest that zinc supplementation may improve glucose handling in subjects with prediabetes. A 2015 systematic review identified three short trials (4 to 12 weeks) conducted in adults with prediabetes and found little evidence of an improvement in insulin resistance with zinc supplementation (103). However, a 2016 randomized, placebo-controlled trial in 55 Bangladeshi with prediabetes showed that daily supplementation with zinc sulfate (30 mg/day for 6 months) improved fasting blood glucose, as well as measures of β-cell function and insulin sensitivity (104). Similar observations were made in another recent trial in 100 Sri Lankan randomized to receive daily supplementation with zinc (20 mg of elemental zinc) or a placebo for one year (105). Supplemental zinc improved zinc status and measures of glycemic control (105). Large-scale, long-term studies are necessary to provide definite conclusions regarding the potential benefit of zinc supplementation in subjects at risk of type 2 diabetes.

Disease Treatment

Doses of supplemental zinc in many of the below-mentioned clinical trials exceeded the tolerable upper intake level (UL). Such high intake of supplemental zinc may lead to adverse health effects with prolonged use (see Safety).

Wilson's disease

The protein, ATP7B, is responsible for the excretion of hepatic copper into the biliary tract, and its impairment in Wilson's disease results in an increased concentration of 'free' copper (i.e., not bound to the copper-carrying protein, ceruloplasmin) in blood, an increased excretion of copper in the urine (hypercupriuria), the deposition of copper in part of the cornea (forming Kayser-Fleischer rings), and the accumulation of copper in the liver and brain (106). This inherited condition is progressive and fatal if untreated. The standard-of-care for symptomatic patients usually includes an initial phase (around 2-6 months) of copper chelation with agents, such as penicillamine or trientine (triethylenetetramine), followed by lifelong maintenance therapy with penicillamine and/or trientine and/or zinc salts (107). Patients presenting without symptoms can be treated with maintenance therapeutic doses of a chelating agent or with zinc (108). Zinc-induced metallothionein in the intestinal mucosa binds copper and prevents its absorption (see Nutrient interactions). There is growing evidence to suggest that zinc salts are a safer, much cheaper, and efficacious alternative to metal-chelating agents — which have been associated with a worsening of symptoms during the initial phase of treatment in some patients (109). The use of zinc is advocated as safe and efficacious in both pediatric (110, 111) and adult patients (112-114).

Common cold

Zinc lozenges

There is no proven treatment for common cold (115). The use of zinc lozenges within 24 hours of the onset of cold symptoms, and continued intake every two to three hours while awake until symptoms resolve, have been advocated for reducing the duration of the common cold (116). Several clinical trials examining the effect of zinc have been published to date. A 2012 systematic review and meta-analysis of 13 randomized controlled trials reported that zinc supplementation in the form of lozenges or syrup shortened the duration of cold symptoms, but there was significant heterogeneity (inconsistent effects across the included studies) for the primary outcomes (117). A 2013 Cochrane review confirmed that oral zinc administrated within 24 hours of symptom onset could reduce the duration of cold symptoms (14 trials, 1,656 participants) (118). Subgroup analyses also suggested that oral zinc was effective regardless of the age of participants (children or adults) and the type of zinc formulation (gluconate/acetate lozenges or sulfate syrup). In addition, beneficial effects on cold duration were seen in trials that provided more than 75 mg/day of zinc but not in trials that used lower doses. The pooled analysis of five trials found no evidence of an effect of oral zinc on the severity of cold symptoms. The analysis of secondary trial outcomes suggested a faster resolution of specific cold symptoms (cough, nasal congestion, nasal drainage, sore throat) and a lower proportion of participants exhibiting cold symptoms after seven days of treatment in zinc- versus placebo-supplemented participants (118).

Inconsistent findings among trials have been partly attributed to different amounts of zinc released from various forms used in the lozenges (particularly zinc acetate and zinc gluconate) (119, 120). It has been argued that the unpleasant taste of zinc gluconate forming complexes with carbohydrates may have led to poor compliance, thereby explaining negative trial results (119, 121). However, when a meta-analysis was recently conducted on results from seven trials (575 participants) that employed zinc lozenges at doses >75 mg/day, there was no evidence of a difference in efficacy observed between trials that used either zinc acetate (3 trials) or zinc gluconate (4 trials) (122).

With numerous well-controlled trials and meta-analyses, the efficacy of zinc lozenges or syrup in treating common cold symptoms is no longer questionable. A meta-analysis of seven trials recently reported a 33% reduction in the duration of cold symptoms with the intake of zinc lozenges (>75 mg/day of elemental zinc) (122). However, many supplemental zinc formulations available over-the-counter have been found to release zero zinc ions (i.e., the biologically active form of zinc) or to contain additives (e.g., magnesium, certain amino acids, citric acid) that either cancel out the benefit of zinc or worsen cold symptoms (119).

Finally, although taking zinc lozenges for a cold every two to three hours while awake will result in daily zinc intakes well above the tolerable upper intake level (UL) of 40 mg/day for adults (see Safety), the use of zinc at daily doses of 50 to 180 mg for one to two weeks has not resulted in serious side effects (117). Bad taste and nausea were the most frequent adverse effects reported in therapeutic trials (117). Use of zinc lozenges for prolonged periods (e.g., 6-8 weeks) is likely to result in copper deficiency (see Nutrient interactions and Safety).

Intranasal zinc (zinc nasal gels and nasal sprays)

Intranasal zinc preparations, designed to be applied directly to the nasal epithelium (cells lining the nasal passages), are marketed as over-the-counter cold remedies. While two placebo-controlled trials found that intranasal zinc gluconate modestly shortened the duration of cold symptoms (123, 124), another one found intranasal zinc to be of no benefit (125). The pooled analysis of these three trials showed no overall benefit of intranasal zinc on the risk of still experiencing cold symptoms by day 3 (126). The existence of a mouth-nose biologically close electric circuit (BCEC) has been proposed to explain the efficacy of oral rather than intranasal zinc delivery (119). Specifically, it is suggested that the positively charged interior of the nose repels ionic zinc (Zn^{2+}) such that ionic zinc delivered by throat lozenges and migrating from the mouth to the nose are more effective against rhinovirus infection than those directly delivered into the nose (119). Of serious concern are several case reports of individuals experiencing loss of the sense of smell (anosmia) after using intranasal zinc as a cold remedy (127). Since zinc-associated anosmia may be irreversible, intranasal zinc preparations should be avoided.

Age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative disease of the macula and a leading cause of blindness in people aged >65 years in the US (128). The macula is the portion of the retina in the back of the eye involved with central vision. Zinc is hypothesized to play a role in the development of AMD for several reasons: (1) zinc is found at high concentrations in the part of the retina affected by AMD, (2) retinal zinc content has been shown to decline with age, and (3) the activities of some zinc-dependent retinal enzymes have been shown to decline with age. To date, prospective cohort studies have shown limited evidence suggesting an association between dietary zinc intake and the incidence of AMD (129-131).

However, an early randomized controlled trial provoked interest when it found that 200 mg/day of zinc sulfate (81 mg/day of elemental zinc) over two years limited the loss of vision in patients with AMD (132). Yet a later trial using the same dose and duration found no benefit to patients with a more advanced form of AMD in one eye (133). Small trials have generally not reported a protective effect of vitamin and mineral supplementation on AMD (134, 135). However, a randomized, double-blind, placebo-controlled trial in 74 patients with AMD reported that supplementation with 50 mg/day of zinc monocysteine for six months improved measures of macular function, including visual acuity, contrast sensitivity, and photorecovery (136). A large randomized, placebo-controlled trial of daily supplementation with antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of β-carotene) and high-dose zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide) — the Age-Related Eye Disease Study (AREDS) — found that administration of high-dose zinc alone or with the antioxidant combination to individuals with signs of moderate-to-severe macular degeneration significantly reduced the risk of developing advanced macular degeneration over a mean follow-up of 6.3 years (137). A follow-up analysis conducted four years after the cessation of the trial in 2001, including nearly 85% of the surviving participants, found that the benefit of the AREDS (combined antioxidants plus zinc) formulation had persisted (138). Indeed, the odds of developing late AMD, especially neovascular AMD, was lower in both participants with a low risk of developing AMD and those who were at risk and recommended to continue taking the AREDS formulation after the trial ended. There was, however, no effect of AREDS formulation on the risk of developing central geographic atrophy (138). Another trial, AREDS2, examined the effect of an AREDS formulation without β-carotene and/or containing 25 mg instead of 80 mg of zinc (139). The trial showed no apparent difference in the risk of developing advanced AMD with the use of AREDS formulations containing either 25 mg or 80 mg of zinc and/or β-carotene (140). A recent meta-analysis of five trials (including the original AREDS study) confirmed the protective effect of supplemental zinc against neovascular and advanced AMD (141).

In conclusion, the AREDS formulation combining antioxidants and zinc (25 mg or 80 mg) may delay the progression of the disease in patients with AMD. Patients, especially smokers and those with vascular disease, are advised to discuss with their physician the benefits versus potential harms that could be associated with the long-term use of high-dose antioxidant vitamins and carotenoids (141).

Diabetes mellitus

Type 2 diabetes mellitus

Poor glycemic control and frequent urination in patients with diabetes mellitus may be driving urinary loss of zinc and contribute to marginal zinc deficiency (142, 143). Yet, because of the role of zinc in β-cell function and insulin action (see Disease Prevention), a number of randomized controlled trials have examined whether supplementation with zinc (alone or with other minerals and vitamins) could play a role in diabetes management, especially by improving glycemic control in people with type 2 diabetes (15). Out of the 12 trials that measured participants' zinc status at baseline, supplementation with zinc (20-240 mg/day) for 4 to 16 weeks improved fasting blood glucose in patients who presented with zinc deficiency (6 studies). Supplemental zinc also reduced the proportion of glycated hemoglobin (HbA1c) in two trials conducted in zinc-deficient participants, yet not in four studies including participants without zinc deficiency (15). Patients with type 2 diabetes should ensure that their diet provides enough zinc to cover their needs, especially if their blood glucose is poorly controlled.

Gestational diabetes mellitus

Gestational diabetes mellitus is defined as hyperglycemia that is first diagnosed during pregnancy. The condition is associated with an increased risk for adverse pregnancy outcomes (144). A group of investigators in Iran conducted two small randomized, placebo-controlled trials to examine the effect of zinc supplementation in pregnant women with gestational diabetes. Supplemental zinc (30 mg/day) for six weeks during pregnancy improved zinc status, reduced fasting blood glucose, and improved insulin sensitivity in women with gestational diabetes but had no impact on pregnancy outcomes, including the need for cesarean section, need for insulin therapy, newborn's birth size and Apgar scores, or incidence of hyperbilirubinemia (145, 146). Similar improvements of markers of glycemic control were reported in another placebo-controlled trial that randomized pregnant women with gestational diabetes to receive zinc (4 mg) together with magnesium (100 mg), calcium (400 mg), and vitamin D (200 IU) twice a day for six weeks (147). There was also some evidence suggesting that supplemental zinc might help correct other metabolic disorders (e.g., abnormal blood lipid profile) associated with gestational diabetes (147, 148).

HIV/AIDS

Sufficient zinc is essential to maintain immune system function, and HIV-infected individuals are particularly susceptible to zinc deficiency. In HIV-infected patients, low serum zinc concentrations have been associated with disease progression and increased mortality (149, 150). In one study conducted in AIDS patients, 45 mg/day of zinc for one month resulted in a decreased incidence of opportunistic infections compared to placebo (151). A placebo-controlled trial in 231 HIV-positive adults with low zinc status found that zinc supplementation (12 mg/day for women and 15 mg/day for men) for 18 months reduced the incidence of immunological failure (defined by a $CD4^+$ count <200 cells/mm^3) by 76% and the rate of diarrhea by 60% (152). A 2011 systematic review that identified three randomized controlled trials in primarily resource-poor settings concluded that zinc supplementation was safe and efficacious in reducing opportunistic infections in HIV-positive adults (153).

Evidence of benefits of zinc supplementation in HIV-positive pregnant women and children is very limited. In a double-blind, randomized, placebo-controlled trial in Tanzania, the administration of zinc (25 mg/day) to women between 12 and 27 weeks' gestation until six months after delivery failed to reduce maternal viral load or limit mother-to-child HIV transmission (154). A randomized placebo-controlled trial of zinc supplementation (10 mg/day for 6 months) in 96 HIV-positive children (6 months to 5 years old) in South Africa showed no effect on $CD4^+$ count and viral load (155). There was evidence showing a reduction in the incidence of watery diarrhea in zinc-supplemented children compared to those taking a placebo, yet no differences in the incidence of pneumonia, ear infection, or upper respiratory tract infection (155). Another trial in Uganda showed that supplemental zinc in children with severe pneumonia effectively reduced case fatality regardless of children's HIV status (156). While zinc supplementation during pregnancy and infancy is recommended in populations likely to be zinc deficient (43, 71, 75), its use in HIV infection management requires further investigation (157).

Alzheimer's disease

Abnormal homeostasis of trace metals, in particular copper and zinc, has been reported in individuals affected by Alzheimer's disease — the most common form of dementia. Specifically, results from case-control studies have shown higher serum copper concentrations and lower serum zinc concentrations in people with Alzheimer's disease compared to cognitively healthy controls (158-160). Based on the utilization of zinc salts in Wilson's disease, it has been proposed that zinc supplementation could improve zinc and copper status and limit further cognitive deterioration in individuals with Alzheimer's disease. The use of slow-release zinc acetate (150 mg/day for six months) in a randomized, placebo-controlled study of 60 patients with mild-to-moderate Alzheimer's disease corrected low zinc status and decreased serum 'free' copper (i.e., unbound to ceruloplasmin) (161). Moreover, when a post-hoc analysis was restricted to participants over 70 years of age (N=29), it was found that zinc supplementation prevented the deterioration of cognition scores over the trial period (161). Additional evidence is needed to confirm whether zinc supplementation could play a role in stabilizing cognitive deficits in older adults with dementia.

Depression

A data analysis of the Boston Area Community Health (BACH) survey, including 3,708 participants (ages, 30-79 years), reported higher odds of depression symptoms in women (but not in men) in the lowest versus highest quartiles of total (median values, 8.7 mg/day versus 26.8 mg/day) and dietary (median values, 7.6 mg/day versus 13.1 mg/day) zinc intakes (162). The possibility that zinc could play a role in preventing or alleviating depression has been explored in two trials conducted by one research group. The data from these trials were analyzed following a per-protocol approach (i.e., restricted to the participants who completed the studies). A preliminary randomized, double-blind, placebo-controlled trial in 20 subjects (mean age, 43 years) treated for major depression showed that supplementation with 25 mg/day of zinc reduced depression symptoms at 6 and 12 weeks as assessed by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores (163). A second placebo-controlled trial in 60 participants treated with the antidepressant imipramine (Tofranil; 100-200 mg/day) assessed the therapeutic response to supplemental zinc (25 mg/day) using HDRS, BDI, Clinical Global Impression scale (CGI), and Montgomery-Åsberg Depression Rating Scale (MADRS) scores (164). Zinc supplementation improved score-based measures of therapeutic response and remission after six weeks but only when the analysis was restricted to participants resistant to imipramine. There was, however, no evidence of an effect of zinc after 12 weeks (164).

Neonatal sepsis

Sepsis is a life-threatening condition that causes organ dysfunction as a consequence of a dysregulated host's response to infection (165). Sepsis is accompanied by changes in zinc homeostasis characterized in particular by a decrease in serum zinc concentration and an increase in liver zinc concentration (166). These changes in zinc distribution are thought to be part of a host's defense mechanism whereby the host can limit zinc availability to pathogens, as well as stimulate the immune system. Such a mechanism has been described for other transition metals, including iron and manganese (167). However, lower serum zinc concentrations in critically ill patients at high risk of organ failure have been associated with recurrent sepsis episodes and poorer outcomes (168, 169). A 2018 systematic review identified four trials that examined the effect of zinc supplementation in newborns with sepsis (166). Zinc supplementation was found to result in decreased inflammation (170) and better neurological development (171, 172). Three out of four trials that examined the rate of mortality showed no effect of zinc supplementation (170, 172, 173).

Sources

Food sources

Shellfish, beef, and other red meats are rich sources of zinc; nuts and legumes are relatively good plant sources of zinc. Zinc bioavailability (the fraction of zinc retained and used by the body) is relatively high in meat, eggs, and seafood because of the relative absence of compounds that inhibit zinc absorption and the presence of sulfur-containing amino acids (cysteine and methionine) that improve zinc absorption. Zinc in whole-grain products and plant proteins is less bioavailable due to their relatively high content of phytate, which inhibits zinc absorption (174). The enzymatic action of yeast reduces the level of phytate in foods; therefore, leavened whole-grain breads have more bioavailable zinc than unleavened whole-grain breads.

National dietary surveys in the US estimate that average dietary zinc intake from naturally and fortified food is about 12.3 mg/day in adults, with about 12% of the adult population being at risk for inadequate intake (175). The zinc content of some foods relatively rich in zinc is listed in **Table 2** in milligrams (mg). For more information on the nutrient content of specific foods, search USDA's FoodData Central (176).

Table 2. Some Food Sources of Zinc

Food	Serving	Zinc (mg)
Oyster, cooked	6 medium	27-50
Beef, chuck, blade roast, cooked	3 ounces*	8.7
Beef, ground, 90% lean meat, cooked	3 ounces	5.4
Crab, Dungeness, cooked	3 ounces	4.7
Fortified, whole-grain toasted oat cereal	1 cup	3.8
Turkey, dark meat, cooked	3 ounces	3.0
Pork, loin, blade roast, cooked	3 ounces	2.7
Soybeans, dry roasted	½ cup	2.2
Chicken, roasting, dark meat, cooked	3 ounces	1.8
Pine nuts	1 ounce	1.8
Cashews	1 ounce	1.6
Yogurt, plain, low fat	6 ounces	1.5
Sunflower seed kernels	1 ounce	1.5
Pecans	1 ounce	1.3
Brazil nuts	1 ounce	1.2
Chickpeas (garbanzo beans), cooked	½ cup	1.2
Milk	1 cup (8 fl. oz.)	1.1
Cheese, cheddar	1 ounce	1.0
Almonds	1 ounce	0.9
Beans, baked	½ cup	0.9
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

A number of zinc supplements are commercially available, including zinc acetate, zinc gluconate, zinc picolinate, and zinc sulfate. Zinc picolinate has been promoted as a more absorbable form of zinc, but few data support this idea in humans. Limited work in animals suggests that increased intestinal absorption of zinc picolinate may be offset by increased elimination (29).

Safety

Toxicity

Acute toxicity

Isolated outbreaks of acute zinc toxicity have occurred as a result of the consumption of food or beverages contaminated with zinc released from galvanized containers. Signs of acute zinc toxicity are abdominal pain, diarrhea, nausea, and vomiting. Single doses of 225 to 450 mg of zinc usually induce vomiting. Milder gastrointestinal distress has been reported at doses of 50 to 150 mg/day of supplemental zinc. Metal fume fever has been reported after the inhalation of zinc oxide fumes. Specifically, profuse sweating, weakness, and rapid breathing may develop within eight hours of zinc oxide inhalation and persist for 12 to 24 hours after exposure is terminated (6, 29).

Adverse effects

The major consequence of long-term consumption of excessive zinc is copper deficiency. Total zinc intakes of 60 mg/day (50 mg supplemental and 10 mg dietary zinc) for up to 10 weeks have been found to result in signs of copper deficiency (29). Copper deficiency has also been reported following chronic use of excessive amounts of zinc-containing denture creams (≥2 tubes per week containing 17-34 mg/g of zinc) (177). In order to prevent copper deficiency, the US Food and Nutrition Board set the tolerable upper intake level (UL) for adults at 40 mg/day, including dietary and supplemental zinc (**Table 3**) (29).

Table 3. Tolerable Upper Intake Level (UL) for Zinc

Age Group	UL (mg/day)
Infants 0-6 months	4
Infants 7-12 months	5
Children 1-3 years	7
Children 4-8 years	12
Children 9-13 years	23
Adolescents 14-18 years	34
Adults 19 years and older	40

Intranasal zinc

Intranasal zinc is known to cause a loss of the sense of smell (anosmia) in laboratory animals (178), and there have been several case reports of individuals who developed anosmia after using intranasal zinc gluconate (127). Since zinc-associated anosmia may be irreversible, the use of zinc nasal gels and sprays should be avoided.

Drug interactions

The use of zinc supplements decreases the absorption of certain medications, including cephalexin (Keplex) and penicillamine (Cuprimine, Depen), as well as the antiretroviral drugs atazanavir (Reyataz) and ritonavir (Norvir) (179). Concomitant administration of zinc supplements with certain medications like tetracycline and quinolone antibiotics may decrease the absorption of both zinc and the medications, potentially reducing drug efficacy. Taking zinc supplements and these medications at least two hours apart should prevent this interaction.

The therapeutic use of metal-chelating agents, such as penicillamine (used to treat copper overload in Wilson's disease) and diethylenetriamine pentaacetate (DTPA; used to treat iron overload), has resulted in severe zinc deficiency. Anticonvulsant drugs, especially sodium valproate, may also precipitate zinc deficiency. Prolonged use of diuretics may increase urinary zinc excretion, resulting in increased loss of zinc. Because supplemental zinc can lower blood glucose, those taking anti-diabetic agents are advised to use zinc supplements with caution.

Linus Pauling Institute Recommendation

The RDA for zinc (8 mg/day for adult women and 11 mg/day for adult men) appears sufficient to prevent deficiency in most individuals, but the lack of sensitive indicators of zinc nutritional status in humans makes it difficult to determine the level of zinc intake most likely to promote optimum health. Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement will generally provide at least the RDA for zinc. Daily total (supplemental + dietary) intakes of zinc should not exceed the UL (40 mg/day for adults) in order to limit the risk of copper deficiency in particular (see Safety).

Older adults (>50 years)

Although the requirement for zinc is not known to be higher for older adults, many have inadequate dietary zinc intakes (180, 181). A reduced capacity to absorb zinc, increased likelihood of disease states that alter zinc utilization, and increased use of drugs that decrease zinc bioavailability may all contribute to an increased risk of mild zinc deficiency in older adults. Adequate dietary intake of zinc is essential for older adults because the consequences of mild zinc deficiency, such as impaired immune system function, are especially relevant to maintenance of their health.

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Other Nutrients

The Food and Nutrition Board of the US Institute of Medicine has set an Adequate Intake level for choline, essential fatty acids (linoleic acid and α-linolenic acid), and total fiber. Select a nutrient from the list for more information.

- Choline
- Essential Fatty Acids
- Fiber

Choline

Contents

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Español

Summary

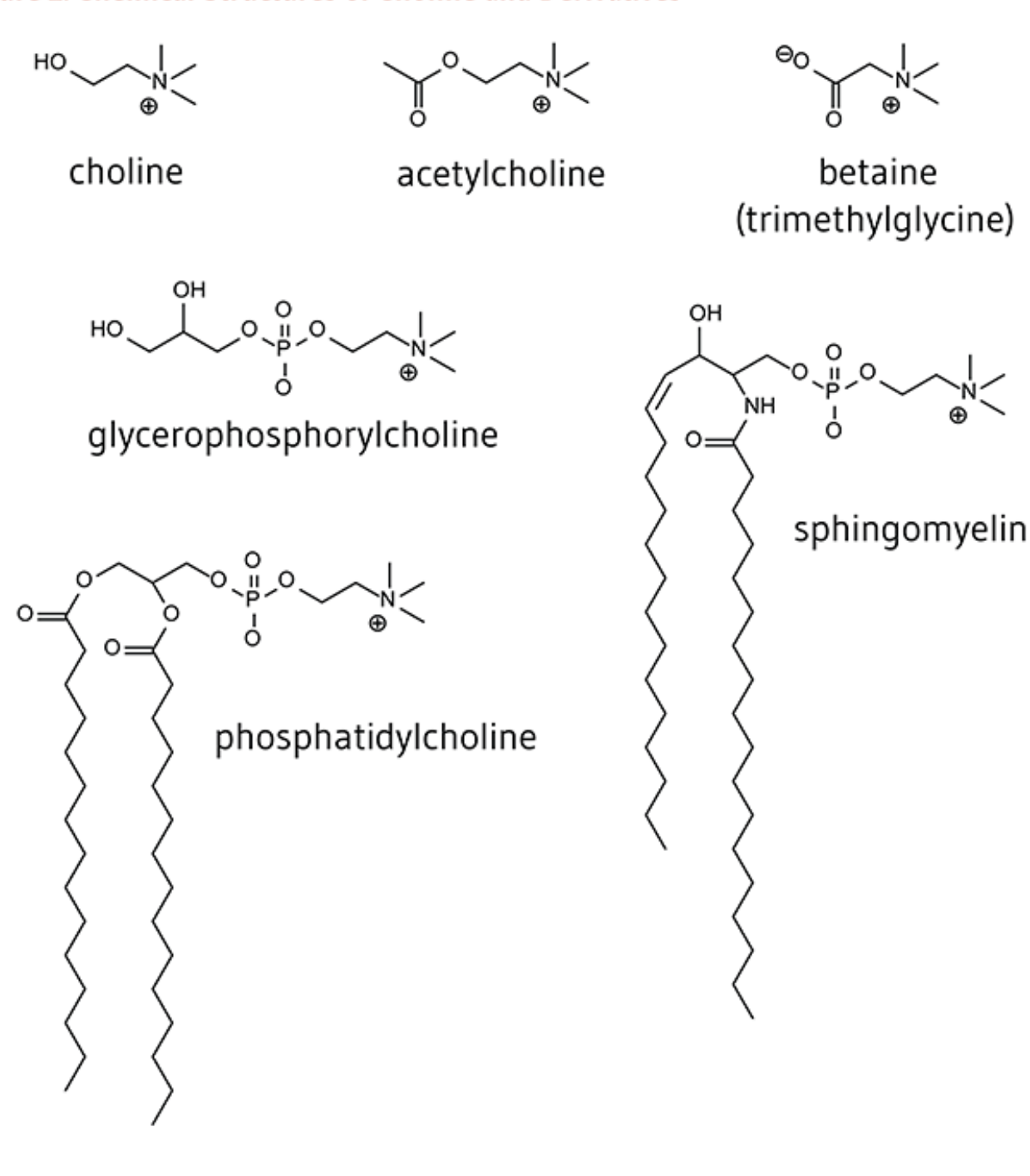
- Choline is a vitamin-like essential nutrient and a methyl donor involved in many physiological processes, including normal metabolism and transport of lipids, methylation reactions, and neurotransmitter synthesis. *(More information)*
- Choline deficiency causes muscle damage and abnormal deposition of fat in the liver, which results in a condition called nonalcoholic fatty liver disease. Genetic predispositions and gender can influence individual variation in choline requirements and thus the susceptibility to choline deficiency-induced fatty liver disease. *(More information)*
- The recommended adequate intake (AI) of choline is set at 425 milligrams (mg)/day for women and 550 mg/day for men. *(More information)*
- Choline is involved in the regulation of homocysteine concentration in the blood through its metabolite betaine. There is currently no convincing evidence that high choline intakes could benefit cardiovascular health through lowering blood homocysteine. Besides, elevated blood concentrations of trimethylamine N-oxide (TMAO), generated from choline, may increase the risk of cardiovascular events. *(More information)*
- The need for choline is probably increased during pregnancy. Case-control studies examining the relationship between maternal choline status and risk of neural tube defects (NTDs) have given inconsistent results. It is not yet known whether periconceptual choline supplementation could confer protection against NTDs. *(More information)*
- Animal studies have shown that choline is essential for optimal brain development and influences cognitive function in later life. However, in humans, there is not enough evidence to assert that choline supplementation during pregnancy improves offspring's cognitive performance or that it helps prevent cognitive decline in older people. *(More information)*
- Recent intervention studies have found that supplementation with citicoline (a choline derivative) may be useful to limit neurologic damage in stroke patients and improve retinal function in some glaucoma patients. It remains unclear whether citicoline could be used in the treatment of dementias and in head trauma patients. *(More information)*
- *De novo* choline synthesis in humans is not sufficient to meet their metabolic needs. Good dietary sources of choline include eggs, meat, poultry, fish, cruciferous vegetables, peanuts, and dairy products. *(More information)*
- Excessive consumption of choline (≥7,500 mg) has been associated with blood pressure lowering, sweating, fishy body odor, and gastrointestinal side effects. The tolerable upper intake level (UL) for adults is 3,500 mg/day. *(More information)*

Although choline is not by strict definition a vitamin, it is an essential nutrient. Despite the fact that humans can synthesize it in small amounts, choline must be consumed in the diet to maintain health. The majority of the body's choline is found in specialized fat molecules known as phospholipids, the most common of which is called phosphatidylcholine (1).

Function

Choline and compounds derived from choline (i.e., metabolites) serve a number of vital biological functions (**Figure 1**) (1).

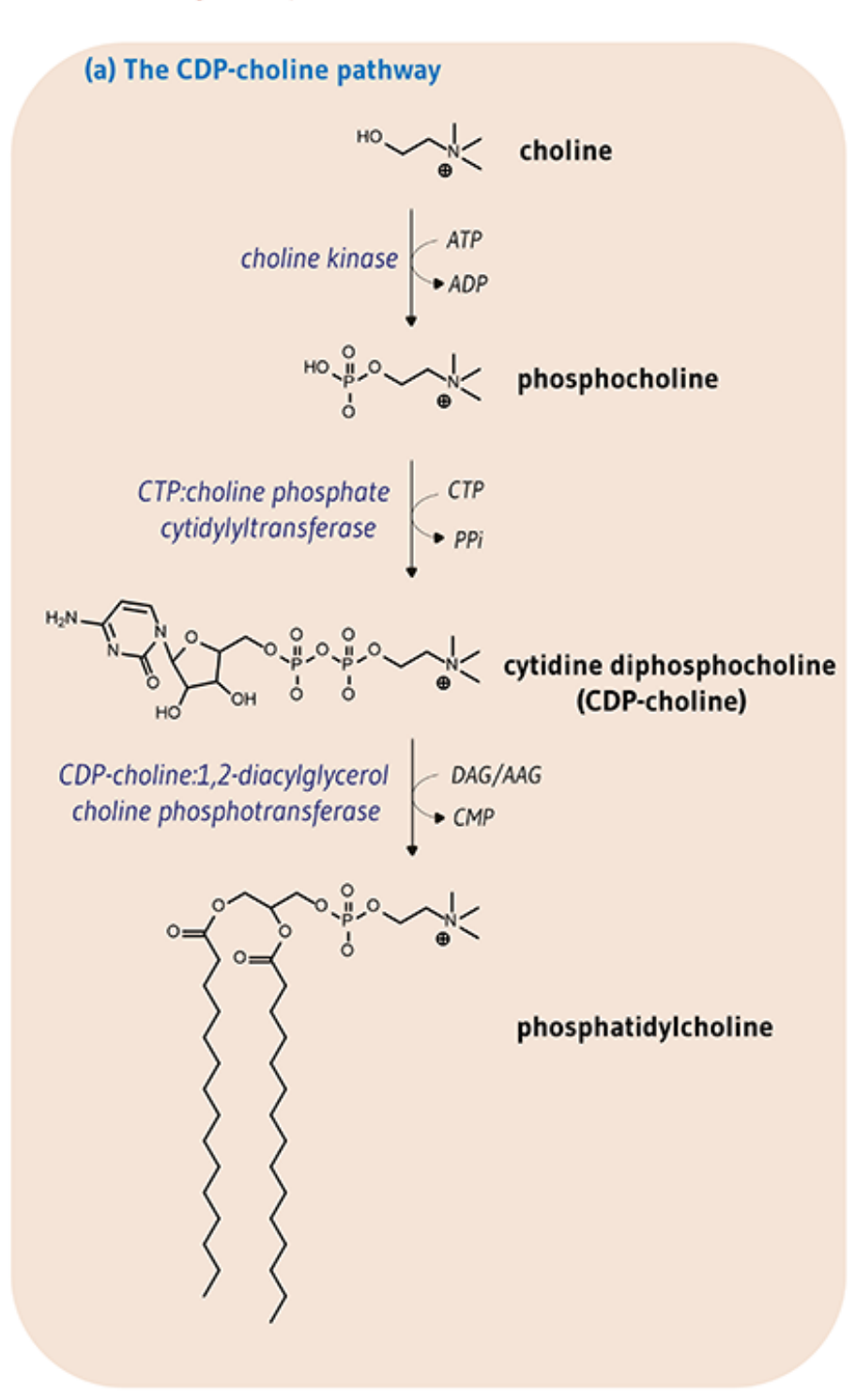
Figure 1. Chemical Structures of Choline and Derivatives



Structural integrity of cell membranes

Choline is used in the synthesis of certain phospholipids (phosphatidylcholine and sphingomyelin) that are essential structural components of cell membranes. Phosphatidylcholine accounts for about 95% of total choline in tissues (2). This phospholipid can be synthesized from dietary choline via the cytidine diphosphocholine (CDP-choline) pathway or through the methylation of another phospholipid, phosphatidylethanolamine (**Figure 2**) (3). Sphingomyelin is a type of sphingosine-containing phospholipid (sphingolipid) that is synthesized by the transfer of a phosphocholine residue from a phosphatidylcholine to a ceramide (**Figure 3**). Sphingomyelin is found in cell membranes and in the fatty sheath that envelops myelinated nerve fibers.

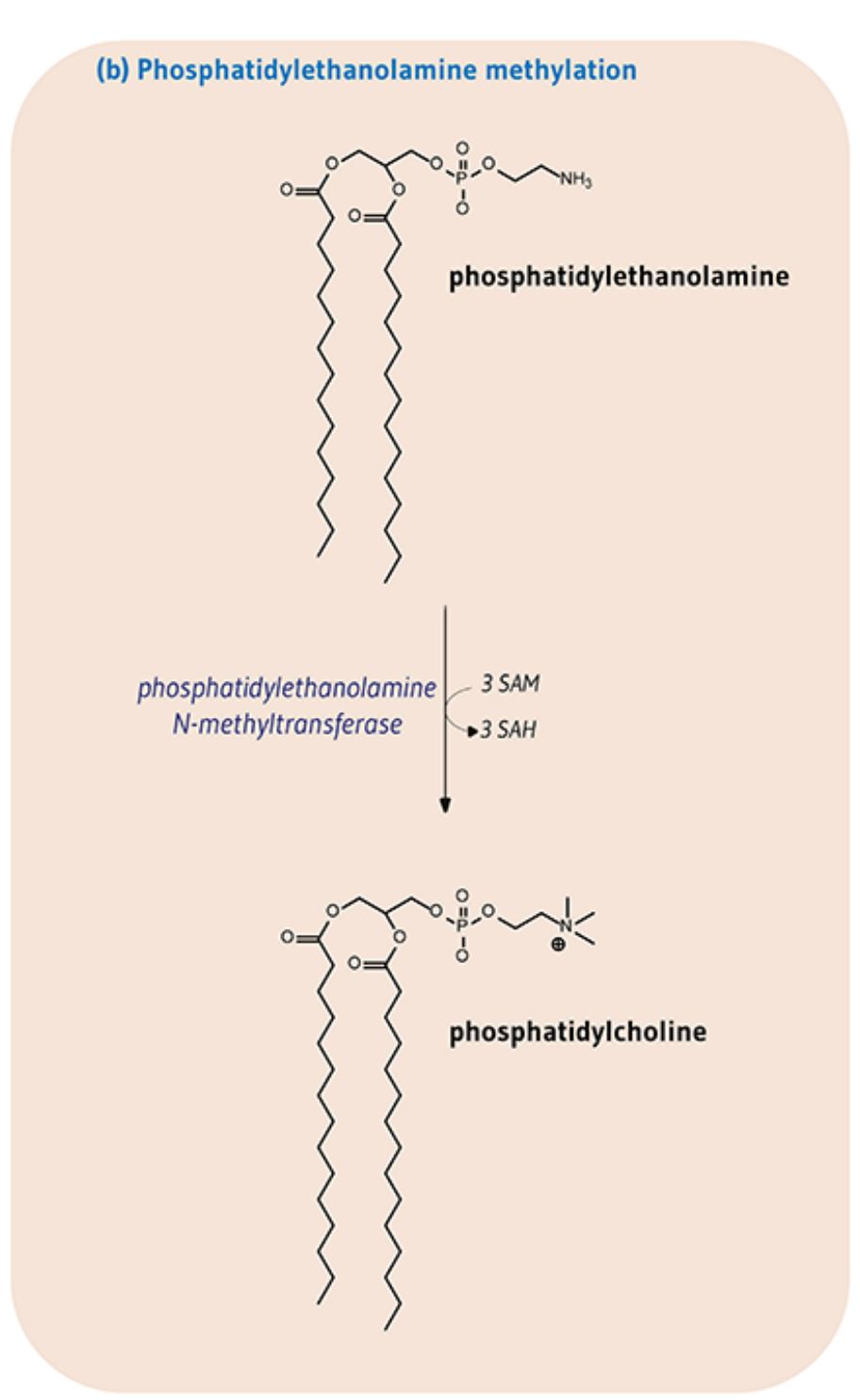
Figure 2a. Synthesis of Phosphatidylcholine



(a) The CDP-choline pathway
choline
choline kinase
ATP
ADP
phosphocholine
CTP:choline phosphate cytidylyltransferase
CTP
PPi
cytidine diphosphocholine (CDP-choline)
CDP-choline:1,2-diacylglycerol choline phosphotransferase
DAG/AAG
CMP
phosphatidylcholine

Phosphatidylcholine is synthesized from choline via the cytidine diphosphocholine (CDP-choline) pathway. *AAG, Alkyl-acylglycerol; ADP/ATP, Adenosine di/triphosphate; CMP/CDP/CTP, Cytidine mono/di/triphosphate; DAG, diacylglycerol; PPi, inorganic pyrophosphate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine.*

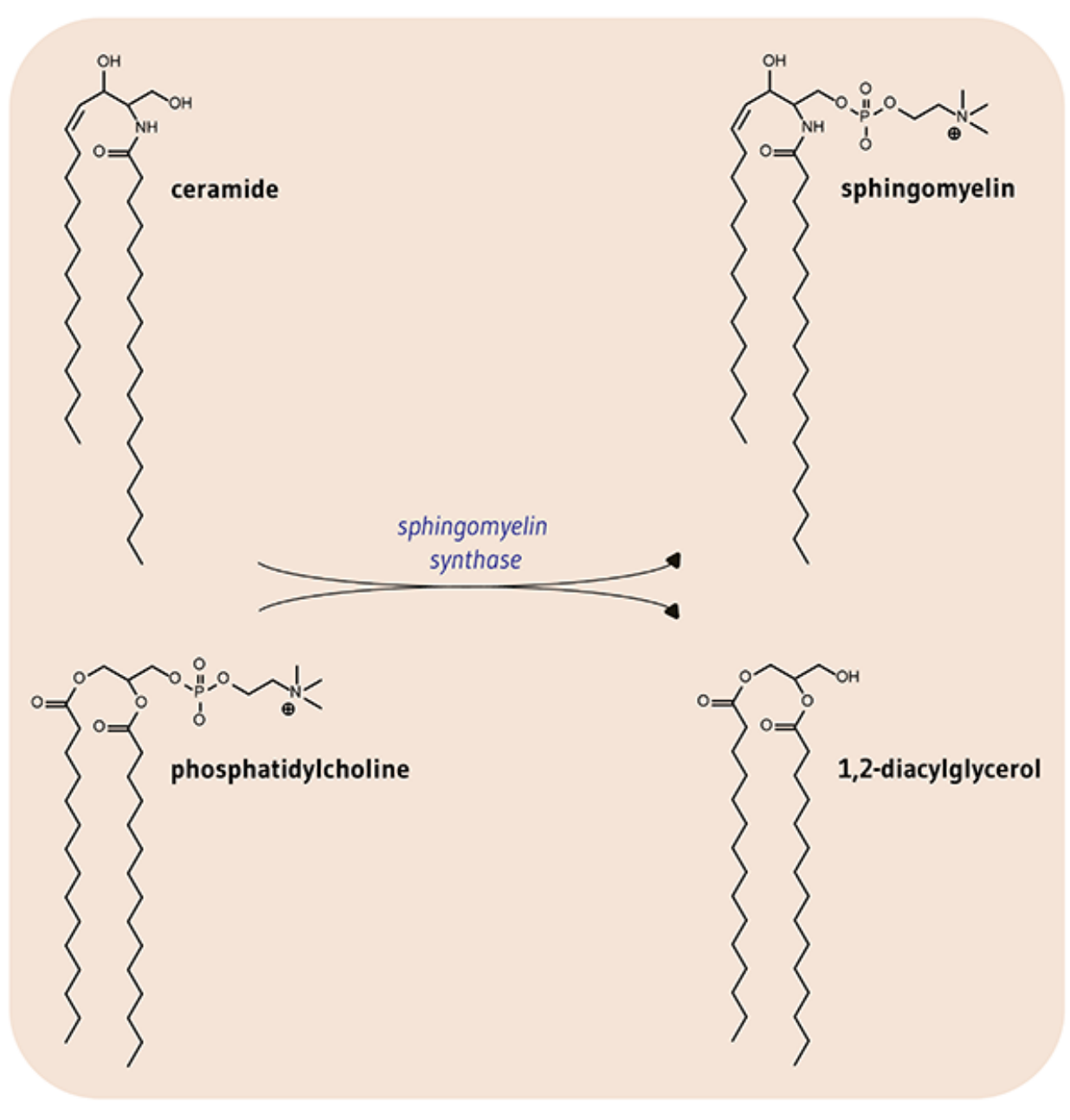
Figure 2b. Synthesis of Phosphatidylcholine



(b) Phosphatidylethanolamine methylation
phosphatidylethanolamine
phosphatidylethanolamine N-methyltransferase
3 SAM
3 SAH
phosphatidylcholine

Phosphatidylcholine is synthesized from choline through the methylation of another phospholipid called phosphatidylethanolamine. *AAG, Alkyl-acylglycerol; ADP/ATP, Adenosine di/triphosphate; CMP/CDP/CTP, Cytidine mono/di/triphosphate; DAG, diacylglycerol; PPi, inorganic pyrophosphate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine.*

Figure 3. Synthesis of Sphingomyelin



Sphingomyelin synthase catalyzes the transfer of a phosphocholine headgroup from phosphatidylcholine to ceramide, generating sphingomyelin and 1,2-diacylglycerol.

Cell signaling

The choline-containing phospholipids, phosphatidylcholine and sphingomyelin, are precursors for the intracellular messenger molecules, diacylglycerol and ceramide. Specifically, sphingomyelinases (also known as sphingomyelin phosphodiestarases) catalyze the cleavage of sphingomyelin, generating phosphocholine and ceramide. Diacylglycerol is released by the degradation of phosphatidylcholine by phospholipases. Other choline metabolites known to be cell-signaling molecules include platelet activating factor (PAF) and sphingophosphocholine.

Nerve impulse transmission

Choline is a precursor for acetylcholine, an important neurotransmitter synthesized by cholinergic neurons and involved in muscle control, circadian rhythm, memory, and many other neuronal functions. Choline acetyltransferase catalyzes the acetylation of choline to acetylcholine, and acetylcholine esterase hydrolyzes acetylcholine to choline and acetate (4). CDP-choline administration was also found to stimulate the synthesis and release of a family of neurotransmitters derived from tyrosine (i.e., the catecholamines, including noradrenaline, adrenaline, and dopamine) (5). Of note, non-neuronal cells of various tissues and organ systems also synthesize and release acetylcholine, which then binds and stimulates cholinergic receptors on target cells (reviewed in 6).

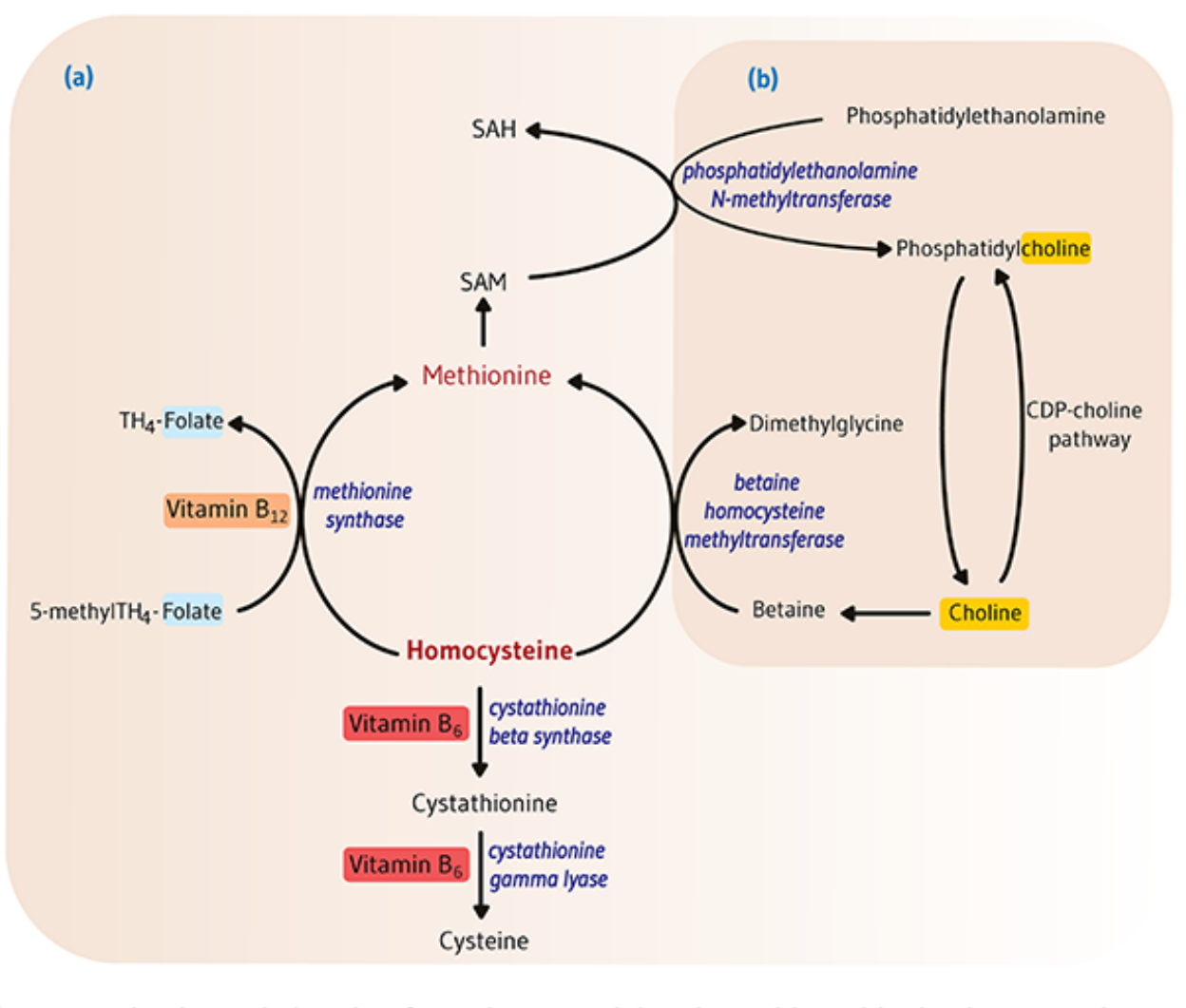
Lipid (fat) transport and metabolism

Fat and cholesterol consumed in the diet are transported to the liver by lipoproteins called chylomicrons. In the liver, fat and cholesterol are packaged into lipoproteins called very-low-density lipoproteins (VLDL) for transport in the bloodstream to extrahepatic tissues. Phosphatidylcholine synthesis by the phosphatidylethanolamine *N*-methyltransferase (PEMT) pathway is required for VLDL assembly and secretion from the liver (7, 8). Without adequate phosphatidylcholine, fat and cholesterol accumulate in the liver (see Deficiency).

Major source of methyl groups

Choline may be oxidized in the liver and kidney to form a metabolite called betaine via a two-step enzymatic reaction. In the mitochondrial inner membrane, flavin adenine dinucleotide (FAD)-dependent choline oxidase catalyzes the conversion of choline to betaine aldehyde, which is then converted to betaine by betaine aldehyde dehydrogenase in either the mitochondrial matrix or the cytosol (2). Betaine is a source of up to 60% of the methyl (CH_3) groups required for the methylation of homocysteine (9). Betaine homocysteine methyltransferase (BHMT) uses betaine as a methyl donor to convert homocysteine to methionine in one-carbon metabolism (**Figure 4**). The ubiquitous vitamin B_{12}-dependent methionine synthase (MS) enzyme also catalyzes the re-methylation of homocysteine, using the folate derivative, 5-methyltetrahydrofolate, as a methyl donor (see Nutrient interactions). Elevated concentrations of homocysteine in the blood have been associated with increased risk of cardiovascular disease (10).

Figure 4. Homocysteine Metabolism



(a) Homocysteine is methylated to form the essential amino acid methionine in two pathways. The reaction of homocysteine remethylation catalyzed by the vitamin B_{12}-dependent methionine synthase captures a methyl group from the folate-dependent one-carbon pool (5-methyltetrahydrofolate). A second pathway requires a choline derivative, betaine (N,N,N-trimethylglycine), as a methyl donor for the methylation of homocysteine catalyzed by betaine homocysteine methyltransferase (BHMT). The catabolic pathway of homocysteine, known as transsulfuration pathway, converts homocysteine to the amino acid cysteine via two vitamin B_6 (PLP)-dependent enzymes: cystathionine β synthase catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionine is then converted to cysteine, α-ketobutyrate, and ammonia by cystathionine γ lyase.

(b) Methionine is the precursor of universal methyl donor, S-adenosylmethionine (SAM). Three SAM molecules are required for the methylation of phosphatidylethanolamine to phosphatidylcholine by phosphatidylethanolamine N-methyltransferase (PEMT). Choline can be generated from phosphatidylcholine via the action of phospholipases. Conversely, choline can be converted to phosphatidylcholine via the cytidine diphospho (CDP)-choline pathway. *TH_4-Folate, Tetrahydrofolate.*

Osmoregulation

The conversion of choline to betaine is irreversible. Betaine is an osmolyte that regulates cell volume and protect cell integrity against osmotic stress (especially in the kidney). Osmotic stress has been associated with a reduced BHMT expression such that the role of betaine in osmoregulation may be temporarily prioritized over its function as a methyl donor (2).

Deficiency

Symptoms

Men and women fed intravenously (IV) with solutions that contained adequate methionine and folate but lacked choline have been found to develop a condition called nonalcoholic fatty liver disease (NAFLD) and signs of liver damage that resolved when choline was provided (11). The occurrence of NAFLD is usually associated with the co-presentation of metabolic disorders, including obesity, dyslipidemia, insulin resistance, and hypertension, in subjects with metabolic syndrome. NAFLD is estimated to progress to a more severe condition called nonalcoholic steatohepatitis (NASH) in about one-third of NAFLD patients, as well as to increase the risk of cirrhosis and liver cancer (12).

Because phosphatidylcholine is required in the synthesis of very-low-density lipoprotein (VLDL) particles (see Function), choline deficiency results in impaired VLDL secretion and accumulation of fat in the liver (steatosis), ultimately leading to liver damage. Because low-density lipoprotein (LDL) particles are formed from VLDL particles, choline-deficient individuals also show reduced blood concentrations of LDL-cholesterol (13). Abnormally elevated biomarkers of organ dysfunction in the blood, including creatine phosphokinase, aspartate aminotransferase, and alanine aminotransferase, are corrected upon choline repletion. Choline deficiency-induced organ dysfunction has also been associated with increased DNA damage and apoptosis in circulating lymphocytes (14). In the liver, the accumulation of lipids is thought to impair mitochondrial function, thus reducing fatty acid oxidation and increasing the production of reactive oxygen species (ROS) that trigger lipid peroxidation, DNA damage, and apoptosis. Further, oxidative stress is thought to be responsible for prompting inflammatory processes that can lead to the progression of NAFLD to NASH and cirrhosis (end-stage liver disease) (15).

An intervention study in 57 healthy adults who were fed choline-deficient diets under controlled conditions found that 77% of men, 80% of postmenopausal women, and 44% of premenopausal women developed fatty liver, liver damage, and/or muscle damage (16). These signs of organ dysfunction resolved upon choline reintroduction in the diet. Because estrogen stimulates the endogenous synthesis of phosphatidylcholine via the phosphatidylethanolamine N-methyltransferase (PEMT) pathway, premenopausal women may be less likely to develop signs of choline deficiency in response to a low-choline diet compared to postmenopausal women (17, 18). Further, a notable single nucleotide polymorphism (SNP; rs12325817) of the *PEMT* gene, which may affect the expression and/or activity of the PEMT enzyme, is thought to increase the susceptibility to choline deficiency-induced organ dysfunction (17). Additional genetic polymorphisms occurring in choline and one-carbon metabolic pathways may alter the dietary requirement for choline and thus increase the likelihood of developing signs of deficiency when choline intake is inadequate (19-21). The composition of one's intestinal microbiota has been recently identified as another potential predictor of susceptibility to choline deficiency-induced NAFLD (22). Of note, intestinal microbiota-dependent metabolism of dietary phosphatidylcholine might also be involved in the pathogenesis of cardiovascular disease (see Safety) (23, 24).

See Disease Prevention for more information on fatty liver diseases.

Nutrient interactions

Together with several B-vitamins (i.e., folate, vitamin B_{12}, vitamin B_6, and riboflavin), choline is required for the metabolism of nucleic acids and amino acids, and for the generation of the universal methyl group donor, S-adenosylmethionine (SAM) (see **Figure 4** above). SAM is synthesized from the essential amino acid, methionine. Three molecules of SAM are required for the methylation reaction that converts phosphatidylethanolamine into phosphatidylcholine (see **Figure 2** above). Once SAM donates a methyl group it becomes S-adenosylhomocysteine (SAH), which is then metabolized to homocysteine. Homocysteine can be converted back to methionine in a reaction catalyzed by vitamin B_{12}-dependent methionine synthase, which requires 5-methyltetrahydrofolate (5-meTHF) as a methyl donor. Alternately, betaine (a metabolite of choline) is used as the methyl donor for the methylation of homocysteine to methionine by the enzyme, betaine-homocysteine methyltransferase (BHMT) (1). Homocysteine can also be metabolized to cysteine via the vitamin B_6-dependent transsulfuration pathway (see **Figure 4** above).

Thus, the human requirement for choline is especially influenced by the relationship between choline and other methyl group donors such as folate and S-adenosylmethionine. A low intake of folate leads to an increased demand for choline-derived metabolite, betaine. Moreover, the *de novo* synthesis of phosphatidylcholine is not sufficient to maintain adequate choline nutritional status when dietary intakes of folate and choline are low (25). Conversely, the demand for folate is increased when dietary supply for choline is limited (26).

The Adequate Intake (AI)

In 1998, the Food and Nutrition Board (FNB) of the Institute of Medicine established a dietary reference intake (DRI) for choline (27). The FNB felt the existing scientific evidence was insufficient to calculate an RDA for choline, so they set an Adequate Intake (AI; **Table 1**). The main criterion for establishing the AI for choline was the prevention of liver damage. Yet, common polymorphisms in genes involved in choline or folate metabolism alter one's susceptibility to choline deficiency and thus may affect dietary requirements for choline (see Deficiency) (17, 19).

Table 1. Adequate Intake (AI) for Choline

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	125	125
Infants	7-12 months	150	150
Children	1-3 years	200	200
Children	4-8 years	250	250
Children	9-13 years	375	375
Adolescents	14-18 years	550	400
Adults	19 years and older	550	425
Pregnancy	all ages	-	450
Breast-feeding	all ages	-	550

Disease Prevention

Cardiovascular disease

Choline and homocysteine

A large body of research indicates that even moderately elevated levels of homocysteine in the blood increase the risk of cardiovascular disease (CVD) (10). The most common cause of a myocardial infarction or a stroke is the rupture of atherosclerotic plaques in arterial walls causing blood clot formation (thrombogenesis). High homocysteine concentrations may promote the development of atherosclerosis (atherogenesis) and thrombogenesis via mechanisms involving oxidative stress and endothelial dysfunction, inflammation, abnormal blood coagulation, and disordered lipid metabolism (reviewed in 28).

Once formed from dietary methionine, homocysteine can be catabolized to cysteine via the transsulfuration pathway or re-methylated to methionine (see **Figure 4** above). Folate and choline are involved in alternate pathways that catalyze the re-methylation of homocysteine (see Nutrient interactions). Specifically, choline is the precursor of betaine, which provides a methyl group for the conversion of homocysteine to methionine via the enzyme, betaine-homocysteine methyltransferase (BHMT). While the amount of homocysteine in the blood is regulated by several nutrients, including folate and choline, conditions that cause damage to the liver like nonalcoholic steatohepatitis (NASH) may also affect homocysteine metabolism (29).

Dietary intakes of choline and betaine and CVD

Because both folate- and choline-dependent metabolic pathways catalyze the re-methylation of homocysteine, dietary intakes of both nutrients need to be considered when the association between homocysteine concentrations and cardiovascular disease is assessed. Yet, despite its relevance, the relationship of betaine and choline to homocysteine metabolism has been only lightly investigated in humans, essentially because the choline content of foods could not be accurately measured until recently. In preliminary intervention studies, pharmacologic doses of betaine (1,500 to 6,000 mg/day) were found to reduce blood homocysteine concentrations in a small number of volunteers with normal-to-mildly elevated homocysteine concentrations (30-33). Yet, in a cross-sectional analysis of a large cohort of 16,165 women (ages, 49-79 years), lower betaine doses in the range of dietary intakes were not found to be correlated with homocysteine concentrations (34). This study also showed that levels of choline intake were inversely associated with homocysteine concentrations in the blood. However, an eight-year follow-up study of the cohort failed to show any difference in cardiovascular risk between women in the upper versus bottom quartile of dietary choline intakes (>329 mg/day vs. ≤266 mg/day) (34). The prospective study of the Atherosclerosis Risk in Communities (ARIC) cohort found that the highest vs. lowest quartile (>486 mg/day vs. <298 mg/day) of total choline intakes from food was not significantly associated with the incidence of coronary artery disease in 14,430 middle-aged participants (35). Also, in a recent analysis of the Health Professionals Follow-up Study (HPFS) that enrolled 44,504 men for a period of 24 years, the risk of peripheral artery disease was positively correlated with homocysteine concentrations but neither with betaine nor choline levels of intake (36).

While further research is indicated, convincing evidence that increased dietary intake of choline or betaine could benefit cardiovascular health through lowering homocysteine concentrations in the blood is presently lacking.

Circulating concentrations of choline and betaine and CVD risk

A 1995 study had found that elevated blood homocysteine concentrations in patients who experienced a vascular occlusion were associated with higher urinary excretion of betaine, rather than with reduced intake of choline or betaine or diminished activity of BHMT (37). In a recent prospective study, high urinary betaine excretion was also associated with increased risk of heart failure in 325 nondiabetic subjects who have been hospitalized for acute coronary syndrome (38). In the same study, both top and bottom quintiles of plasma betaine concentrations were associated with an increased risk of secondary acute myocardial infarction. The findings of another prospective study (the Hordaland Health Study) that followed 7,045 healthy adults (ages, 47-49 years and 71-74 years) suggested that high choline and low betaine plasma concentrations were associated with an unfavorable cardiovascular risk profile (39). Indeed, plasma choline was positively associated with a number of cardiovascular risk factors, such as BMI, percentage body fat, waist circumference, and serum triglycerides, and inversely associated with HDL-cholesterol. On the contrary, plasma betaine was positively correlated to HDL-cholesterol and inversely associated with the above-mentioned risk factors as well as with systolic and diastolic blood pressure. More recent studies now suggest that the blood concentration of trimethylamine N-oxide (TMAO), generated from trimethylamine-containing nutrients like dietary choline, rather than that of choline, might influence the risk of cardiovascular events (see Safety).

It is not yet clear whether concentrations of choline, betaine, and/or TMAO in the blood can predict the risk for cardiovascular disease.

Liver diseases

Fatty liver diseases

While a choline-deficient diet results in organ dysfunction and nonalcoholic fatty liver disease (NAFLD) (see Deficiency; 16), it is not known whether suboptimal dietary choline intakes in healthy subjects may contribute to an increased risk for NAFLD. A cross-sectional analysis of two large prospective studies conducted in China – the Shanghai Women's Health Study and the Shanghai Men's Health Study – including 56,195 people (ages, 40-75 years), was recently conducted to assess the association between dietary choline intakes and self-reported diagnosis of fatty liver disease (40). The highest versus lowest quintile of choline intake (412 mg/day vs. 179 mg/day) was associated with a 28% lower risk of fatty liver disease in normal-weight women, but no association was found in overweight or obese women or in men. Another cross-sectional study of 664 individuals with NAFLD or nonalcoholic steatohepatitis (NASH) also reported that disease severity was inversely correlated with dietary choline intakes in postmenopausal women, but not in premenopausal women, men, or children (41).

Liver cancer

In animal models, dietary choline deficiency has been associated with an increased incidence of spontaneous liver cancer (hepatocellular carcinoma) and increased sensitivity to carcinogenic chemicals (9). A number of mechanisms have been proposed to contribute to the cancer-promoting effects of choline deficiency: (1) enhanced liver cell regeneration and tissue sensitivity to chemical insults; (2) altered expression of numerous genes regulating cell proliferation, differentiation, DNA repair, and apoptosis due to improper DNA methylation; (3) increased likelihood of DNA damage caused by mitochondrial dysfunction-induced oxidative stress; and (4) activated protein kinase C-mediated cell-signaling cascade, eventually leading to an increase in liver cell apoptosis (2). Yet, it is not known whether choline deficiency can increase the susceptibility to cancer in humans (2).

Neural tube defects

It is known that folate is critical for normal embryonic development, and maternal supplementation with folic acid decreases the incidence of neural tube defects (NTDs) (42). NTDs include various malformations, such as lesions of the brain (e.g., anencephaly, encephalocele) or lesions of the spine (spina bifida), which are devastating and usually incompatible with life (43). These defects occur between the 21st and 28th days after conception, a time when many women do not realize that they are pregnant (44). While the protective effect of folate against NTD is well established, only a few studies have investigated the role of other methyl group donors, including choline and betaine, in the occurrence of NTDs. A case-control study (424 NTD cases and 440 controls) found that women in the highest versus lowest quartile of periconceptual choline intake (>498.46 mg/day vs. ≤290.41 mg/day) had a 51% lower risk of an NTD-affected pregnancy (45). However, more recent studies failed to find an inverse relationship between maternal choline intake and risk of NTDs (46, 47). Another case-control study (80 NTD-affected pregnancy and 409 controls) in US women found that the lowest concentrations of serum choline (<2.49 mmol/L) during mid-pregnancy were associated with a 2.4-fold higher risk of NTDs (48). Finally, a more recent study, including 71 NTD-affected pregnancies, 214 pregnancies with non NTD malformations, 98 normal pregnancies in women with prior NTD-affected pregnancies, and 386 normal pregnancies, found no associations between maternal blood concentrations of choline during pregnancy, choline- and folate-related genetic variants, and risk of NTDs (49). However, it is important to note that circulating choline concentrations do not accurately reflect dietary intake of choline.

More research is needed to determine whether supplemental choline could add to the protective effect currently being achieved by periconceptual folic acid supplementation.

Cognitive health

Neuro-cognitive development

Increased dietary intake of cytidine 5'-diphosphocholine (CDP-choline or citicoline, a precursor of phosphatidylcholine; see **Figure 2** above) very early in life can diminish the severity of memory deficits in aged rats (50). Choline supplementation of the mothers of unborn rats, as well as rat pups during the first month of life, led to improved performance in spatial memory tests months after choline supplementation had been discontinued (51). A review by McCann et al. discusses the experimental evidence from rodent studies regarding the availability of choline during prenatal development and cognitive function in the offspring (52).

Because of the importance of DNA methylation in normal brain development, neuronal functions, and cognitive processes (53), methyl donor nutrients like choline are essential for optimal brain functioning. However, clinical evidence to determine whether findings in rodent studies are applicable to humans is currently limited. Recently, the analysis of the Seychelles Child Development Nutrition Cohort study reported a lack of an association between plasma concentrations of choline and its related metabolites and cognitive abilities in 256 five-year-old children. Only plasma betaine concentrations were found to be positively correlated with preschool language test scores (54). Yet, because circulating concentrations of choline are not directly related to dietary choline intakes, the study could not evaluate whether maternal choline intakes influence children's brain development.

Project Viva is an ongoing prospective study that has examined the relationship between daily intakes of methyl donor nutrients in 1,210 women during pregnancy and child cognition at three and seven years postpartum. Maternal intake of choline during the first and/or second trimester of pregnancy was not correlated with measures of cognitive performance in children at age 3 years (55). Another report of the study indicated that upper vs. lower quartile of maternal choline intakes during the second trimester of pregnancy (median intakes, 392 mg/day vs. 260 mg/day) was significantly associated with higher visual memory scores in children aged 7 years old (56). Recently, a small randomized, double-blind, placebo-controlled trial in 99 pregnant women (ages, 21-41 years old) evaluated the effect of choline supplementation during pregnancy and lactation on infants' cognitive function at ages 10 and 12 months (57). The results indicated that maternal choline supplementation (750 mg/day of choline in the form of phosphatidylcholine) from 18 weeks of gestation to 3 months' postpartum provided no cognitive benefits in children regarding short-term visio-spatial memory, long-term episodic memory, and language and global development.

Cognitive function in older adults

Cognitive function, including the domains of memory, speed, and executive function, decline gradually with increasing age. The rate of cognitive decline is also influenced by modifiable risk factors like dietary habits. Deficiency in B-vitamins and elevated homocysteine concentrations in the blood have been associated with cognitive impairments in the elderly. Yet, a recent meta-analysis of 11 trials indicated that homocysteine lowering using B-vitamin supplementation fails to limit cognitive decline or improve cognitive performance in older adults (58). The cross-sectional data analysis of a subgroup of 1,391 volunteers (ages, 36-83 years) from the large Framingham Heart Study Offspring cohort has indicated that dietary choline intake was positively associated with specific cognitive functions, namely verbal memory and visual memory (59). Another cross-sectional study of 2,195 individuals (ages, 70-74 years) from the Hordaland Health Study examined cognitive abilities and blood concentrations of various determinants of circulating homocysteine, including choline and betaine (60). Unlike betaine, high vs. low plasma concentrations of free choline (>8.36 mcmol/L vs. ≤8.36 mcmol/L) were found to be significantly associated with a greater performance at cognitive tests assessing sensory motor speed, perceptual speed, executive function, and global cognition. However, in an earlier intervention study that enrolled 235 elderly individuals (mean age, 81 years old) with or without mild vitamin B_{12} deficiency, baseline concentrations of betaine – but not choline – were found to be positively correlated to test scores evaluating the cognitive domains of construction, sensory motor speed, and executive function (61).

More research is needed to determine the effect of choline on the developing brain and whether choline intakes above the RDA may be useful in the prevention of memory loss or dementia in humans.

Disease Treatment

Cerebrovascular diseases

Cerebrovascular diseases (including stroke and sub-acute ischemic cerebrovascular disease) are the main cause of cognitive impairments in older people. Results from experimental studies have suggested that pharmacological doses of citicoline (CDP-choline) could enhance the metabolism of glucose and the biosynthesis of phospholipids and neurotransmitters, while limiting the degradation of phospholipids in neuronal membranes in models of ischemia and neurodegenerative diseases (reviewed in 62). Many short-term intervention studies in older individuals with vascular diseases have found that therapeutic doses of citicoline given either orally, by intramuscular injection, or by intravenous infusion, resulted in improvements in neuropsychological functions, including cognitive, emotional, and behavioral functions (reviewed in 5).

A six-month, multicenter observational study enrolled 197 stroke subjects (mean age, 81.5 years) with a progressive decline of their mental health and general confusion and/or stupor who were initially administered citicoline for 5 or 10 days (2,000 mg/day, by intravenous infusion) within a four-month period, and then for 21 days (1,000 mg/day, by intramuscular injection), repeated once after a seven-day washout period (63). Citicoline treatment was found to be associated with higher scores on cognitive and functional evaluation scales when compared to baseline measurements. However, only randomized controlled trials would be able to assess whether citicoline is protective against vascular damage and cognitive impairment in elderly adults with complex geriatric symptoms.

The International Citicoline Trial on acUte Stroke (ICTUS) is a multicenter and double-blind study that assessed the effect of supplementing 2,298 patients with acute ischemic stroke with citicoline (2,000 mg/day) or a placebo for six weeks on several functional and neurologic outcomes and on mortality rate (64). The results showed no difference between treatment groups after a 90-day follow-up period. Only subgroup analyses found significant benefits of citicoline in patients older than 70 years, in those with moderate rather than severe strokes, and in those not treated with recombinant tissue plasminogen activator (rtPA; standard-of-care treatment). An earlier meta-analysis of small randomized, placebo-controlled trials had reported a positive impact of citicoline (1,000 mg/day, administered for 28 days to 12 months) on memory and behavior in subjects with cognitive deficits associated with cerebrovascular disorders (65). The effect of citicoline was also evaluated in a recent multicenter, open-label, controlled trial (IDEALE trial) in Italian elderly adults (ages, 65-94 years) with evidence of vascular lesions on neuroradiology and mild-to-moderate cognitive deficits, as assessed by Mini-Mental State Examination (MMSE; scores ≥21) (66). Three hundred and forty-nine participants received oral citicoline (1,000 mg/day) or no treatment for nine months. MMSE scores in citicoline-treated individuals remained unchanged while they significantly deteriorated in untreated patients such that MMSE scores between groups were found to be significantly different after three and nine months of treatment. No significant effect was reported in measures of functional autonomy, mood, and behavioral disorders. Another recent open-label, randomized, controlled trial evaluated the effect of citicoline (1,000 mg/day for 12 months) in 347 subjects (mean age, 67.2 years) who suffered an acute stroke. The results demonstrated that citicoline significantly limited cognitive impairments in the domains of attention and executive functions and temporal orientation at 6 and 12 months post-stroke in treated compared to untreated patients (67).

Neurodegenerative diseases

Dementia

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive cognitive decline and dementia. Dysfunctions in neurotransmitter signaling, affecting cholinergic and dopaminergic pathways in particular, have been involved in the occurrence of cognitive impairments. Deficits in acetylcholine and abnormal phospholipid metabolism have been reported in postmortem studies of the brains of AD patients (11). For these reasons, inhibitors of (acetyl) cholinesterase (which catalyzes the breakdown of acetylcholine) and large doses of lecithin (phosphatidylcholine) have been used to treat patients with dementia due to AD in hopes of raising the amount of acetylcholine available in the brain. While cholinesterase inhibitors have shown positive effects on cognitive functions and measures of clinical global state (68), a systematic review of randomized controlled trials did not find lecithin to be more beneficial than placebo in the treatment of patients with cognitive impairment, vascular dementia, AD, or mixed dementia (69). Limited data are available to assess whether citicoline (CDP-choline) might improve cognitive performance in subjects with AD (70). No recent trial has investigated the effect of citicoline in PD patients.

Glaucoma

Optic neuropathies, including glaucoma, are associated with damage of the optic nerve and loss of visual function. In glaucoma, the progressive deterioration of the optic nerve is caused by loss of a specific neuronal population known as retinal ganglion cells (RGC), such that the condition has been classified as a neurodegenerative disease (71). In a small, double-blind, placebo-controlled study, the effect of citicoline was assessed in 24 subjects affected by open-angle glaucoma and treated with β-blockers. Patients were randomized to follow a therapeutic cycle for a total period of eight years: citicoline (1,000 mg/day, by intramuscular injection) or placebo (β-blockers alone) for a two-month period followed by a four-month washout period (72). Electrophysiological examinations were used to assess the extent of visual dysfunctions, including the simultaneous recordings of Pattern ElectroRetinoGrams (PERG) and Visual Evoked Potentials (VEP). Citicoline was found to enhance retinal function and neural conduction along post-retinal visual pathways, such that responses of the visual cortex to stimuli were significantly improved compared to placebo.

In a similar pilot trial, citicoline efficacy was assessed in 26 volunteers (mean age, 65.4 years) affected by another type of optic neuropathy known as non-arteritic anterior ischemic optic neuropathy (NAION). Oral citicoline (1,600 mg/day) was given for 60 days followed by 60 days of washout, and the therapeutic cycle was repeated once. Compared to placebo, citicoline was found to improve retinal function and post-retinal neural conduction, evidenced by PERG and VEP measures (73). Oral citicoline (four cycles of 500 mg/day for four months followed by a two-month washout period) was also found to significantly reduce the rate of visual field loss and the level of intraocular pressure in 41 patients with progressive glaucoma (74). Larger randomized controlled trials are needed to establish whether citicoline supplementation could be included in the medical treatment of glaucoma.

Traumatic brain injury

For decades, pre-clinical and small clinical studies have investigated the effect of citicoline in the management of patients sustaining a traumatic brain injury (TBI). A systematic review of clinical data suggested that citicoline could hasten the resorption of cerebral edema and improve the recovery of consciousness and neurologic disorders in severe TBI cases (classified by Glasgow Coma Scale [GCS] scores of ≤8). Citicoline also appeared to limit memory deficits and the duration and severity of other post-traumatic symptoms (e.g., headache, dizziness, attention disorder) in TBI patients with mild-to-moderate injuries (GCS scores, 9-15) (reviewed in 5). Although citicoline is currently included in TBI therapeutic regimen in 59 countries, only one multicenter, randomized, double-blind, placebo-controlled trial has recently been conducted in the US. The CiticOline Brain Injury Trial (COBRIT) has enrolled 1,213 patients with mild-to-severe TBI and assessed the effect of enteral or oral citicoline (2,000 mg/day, for 90 days) on functional and cognitive outcomes (measured by components of the TBI Clinical Trials Network Care Battery) (75). No significant benefits of citicoline supplementation over placebo were found at 90 days (end of treatment period) and 180 days. A Cochrane review of the effect of citicoline in the treatment of TBI should be available soon (76).

Sources

De novo synthesis (biosynthesis)

Humans can synthesize choline moieties in small amounts by converting phosphatidylethanolamine into phosphatidylcholine (see **Figure 2** above). Three methylation reactions catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT) are required, each using S-adenosylmethionine (SAM) as a methyl group donor. Choline is generated endogenously when the methylation of phosphatidylethanolamine is coupled with the catabolism of newly formed phosphatidylcholine by phospholipases. This is referred to as *de novo* synthesis of choline. The substitution of choline by serine in the synthesis of phosphatidylserine from phosphatidylcholine by phosphatidylserine synthase-1 also releases choline (4). Because phosphatidylcholine metabolism is a source of endogenous choline, the nutrient was not initially classified as essential (1). Yet, *de novo* choline synthesis in humans is not sufficient to meet their metabolic needs such that healthy humans fed choline-deficient diets develop fatty liver, liver damage, and/or muscle damage (see Deficiency).

Food sources

In the US, mean dietary intakes of choline are well below the recommended AI. According to a US national survey, NHANES 2007-2008, mean dietary intakes of choline were approximately 260 mg/day for women and 396 mg/day for men (77). In a 14-year US prospective study, including over 14,000 middle-aged participants, mean daily intakes of choline were 294 mg and 332 mg in women and men, respectively (35). Eggs, liver, and peanuts, are especially rich in choline (27). Major contributors to choline in the American diet are meat, poultry, fish, dairy foods, pasta, rice, and egg-based dishes (77). Spinach, beets, wheat, and shellfish are also good sources of the choline metabolite, betaine (78). Betaine cannot be converted back to choline but can spare some choline requirements for homocysteine remethylation (1). Phosphatidylcholine, which contains about 13% choline by weight, is the main form of choline in dietary products (79). Lecithin extracts, which comprise a mixture of phosphatidylcholine and other phospholipids, are often added during food processing. Lecithins in processed food have been estimated to increase the daily consumption of phosphatidylcholine by about 1.5 mg/kg of body weight for adults (27).

Strict vegetarians, who consume no meat, milk, or eggs, may be at risk for inadequate choline intake. The total choline contents of some choline-containing foods are listed in milligrams (mg) in **Table 2**. For more information on the nutrient content of specific foods, search the USDA food composition website or the USDA documentation on the choline content of common foods.

Table 2. Some Food Sources of Choline

Food	Serving	Total Choline (mg)
Beef liver, pan fried	3 ounces*	356
Wheat germ, toasted	1 cup	202
Egg	1 large	147
Beef, trim cut, cooked	3 ounces	97
Scallop, cooked, steamed	3 ounces	94
Salmon, pink, canned	3 ounces	75
Chicken, breast, cooked, roasted	3 ounces	73
Atlantic cod, cooked	3 ounces	71
Shrimp, canned	3 ounces	69
Brussel sprouts, cooked, boiled	1 cup	63
Broccoli, cooked, boiled	1 cup, chopped	63
Milk, skim	8 fluid ounces	38
Peanut butter, smooth	2 tablespoons	20
Milk chocolate	1.5-ounce bar	20
Peanuts	1 ounce	15
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Supplements

CDP-choline (citicoline) and choline salts, such as choline chloride and choline bitartrate, are available as supplements. Phosphatidylcholine supplements also provide choline; however, choline comprises only about 13% of the weight of phosphatidylcholine (79). Therefore, a supplement containing 4,230 mg (4.23 grams) of phosphatidylcholine would provide 550 mg of choline. Although the term "lecithin" is synonymous with phosphatidylcholine when used in chemistry, commercial lecithins are usually prepared from soybean, sunflower, and rapeseed, and may contain anywhere from 20%-90% of phosphatidylcholine. Egg yolk lecithin is a more unlikely source of lecithin in dietary supplements. Moreover, the nature of phosphatidylcholine-containing fatty acids depends on whether lecithin is produced from vegetable, animal, or microbial sources. In particular, soybean lecithin is richer in polyunsaturated fatty acids than egg yolk lecithin (80).

Safety

Toxicity

High doses (10,000 to 16,000 mg/day) of choline have been associated with a fishy body odor, vomiting, salivation, and increased sweating. The fishy body odor results from excessive production and excretion of trimethylamine, a metabolite of choline. In the inherited condition, primary trimethylaminuria (also known as "fish odor syndrome"; see the article on Riboflavin), a defective flavin containing monooxygenase 3 (FMO3) enzyme results in impaired oxidation of trimethylamine in the liver. Disease management includes the use of choline-restricted diets in affected individuals (81).

Taking large doses of choline in the form of phosphatidylcholine (lecithin) does not generally result in fishy body odor, because its metabolism results in little trimethylamine. A dose of 7,500 mg/day of choline was found to have a slight blood pressure lowering (hypotensive) effect, which could result in dizziness or fainting. Choline magnesium trisalicylate at doses of 3,000 mg/day has resulted in impaired liver function, generalized itching, and ringing of the ears (tinnitus). However, it is likely that these effects were caused by the salicylate, rather than the choline in the preparation (27).

In 1998, the Food and Nutrition Board (FNB) of the Institute of Medicine established the tolerable upper intake level (UL) for choline at 3,500 mg/day for adults (**Table 3**). This recommendation was based primarily on preventing hypotension (low blood pressure), and secondarily, on preventing the fishy body odor due to increased excretion of trimethylamine. The UL was established for generally healthy people, and the FNB noted that individuals with liver or kidney disease, Parkinson's disease, depression, or inherited trimethylaminuria might be at increased risk of adverse effects when consuming choline at levels near the UL (27).

Table 3. Tolerable Upper Intake Level (UL) for Choline

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-8 years	1,000
Children 9-13 years	2,000
Adolescents 14-18 years	3,000
Adults 19 years and older	3,500
*Source of intake should be food and formula only.	

Do high choline intakes and/or phosphatidylcholine supplements increase the risk for cardiovascular disease?

Oral supplementation with phosphatidylcholine (250 mg of total choline from food plus 250 mg of supplemental phosphatidylcholine) has been found to result in detectable concentrations of trimethylamine and trimethylamine N-oxide (TMAO) in the blood (23). The intestinal microbiota is directly implicated in the generation of trimethylamine from dietary choline, phosphatidylcholine, and carnitine. Trimethylamine is subsequently converted into TMAO by flavin-containing monooxygenases in the liver. The prospective study that followed 4,007 individuals,with or without cardiovascular disease (CVD) for a three-year period found baseline concentrations of circulating TMAO to be positively correlated with incidence of death, nonfatal myocardial infarction, and stroke – described as major adverse cardiac events (MACE) (23). In the same cohort, MACE risk was found to be about 30% higher in individuals in the highest vs. lowest quartile of choline or betaine plasma concentrations (82). However, depending on gut microbiota composition, the risk of having an adverse cardiovascular event may be lower in individuals with low vs. high circulating TMAO even though choline and/or betaine concentrations in the blood are elevated (82).

Elevated TMAO concentrations have been reported in subjects at increased risk of CVD, such as those with diabetes mellitus (83) or end-stage renal disease (chronic kidney failure) (84), and in patients with cardiac insufficiency (chronic heart failure) (85). Yet, in the latter patients, high plasma concentrations of choline, betaine, and TMAO were not associated with a poorer survival rate after five years of follow-up (85). Finally, supplementation with choline, TMAO, or betaine was found to result in the formation of macrophage-derived foam cells in atherosclerosis-prone mice (24). Foam cells are known to contribute to the development of atherosclerotic lesions (i.e., atherogenesis) by accumulating excessive amounts of lipids within the arterial walls and triggering the secretion of pro-inflammatory cytokines.

Further research is needed to understand how the composition of intestinal microbiota influences the metabolic fate of ingested choline. At present, there is no evidence that dietary choline increases the risk of cardiovascular events.

Drug interactions

Methotrexate, a medication used in the treatment of cancer, psoriasis, and rheumatoid arthritis, inhibits the enzyme dihydrofolate reductase and therefore limits the availability of methyl groups donated from folate derivatives. Rats given methotrexate have shown evidence of diminished nutritional status of choline and greater drug adverse reactions due to liver dysfunction (11, 86). Thus, individuals taking methotrexate may have an increased choline requirement. Treatments with a family of lipid-lowering drugs known as fibrates (e.g., fenofibrate, bezofibrate) have been associated with an increased excretion of betaine in the urine and a rise in homocysteine concentration in the blood of patients with diabetes mellitus or metabolic syndrome (87, 88). If the benefits of fibrate therapy are indeed mitigated by fibrate-induced betaine deficiency, the use and safety of supplementing patients with betaine would need to be considered (89).

Linus Pauling Institute Recommendation

Little is known regarding the amount of dietary choline required to promote optimum health or prevent chronic diseases in humans. The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 550 mg/day for adult men and 425 mg/day for adult women. A varied diet should provide enough choline for most people, but strict vegetarians who consume no milk or eggs may be at risk of inadequate choline intake.

Older adults (>50 years)

Little is known regarding the amount of dietary choline most likely to promote optimum health or prevent chronic diseases in older adults. At present, there is no evidence to support a different recommended intake of choline from that of younger adults (550 mg/day for men and 425 mg/day for women).

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Essential Fatty Acids

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日本語

Summary

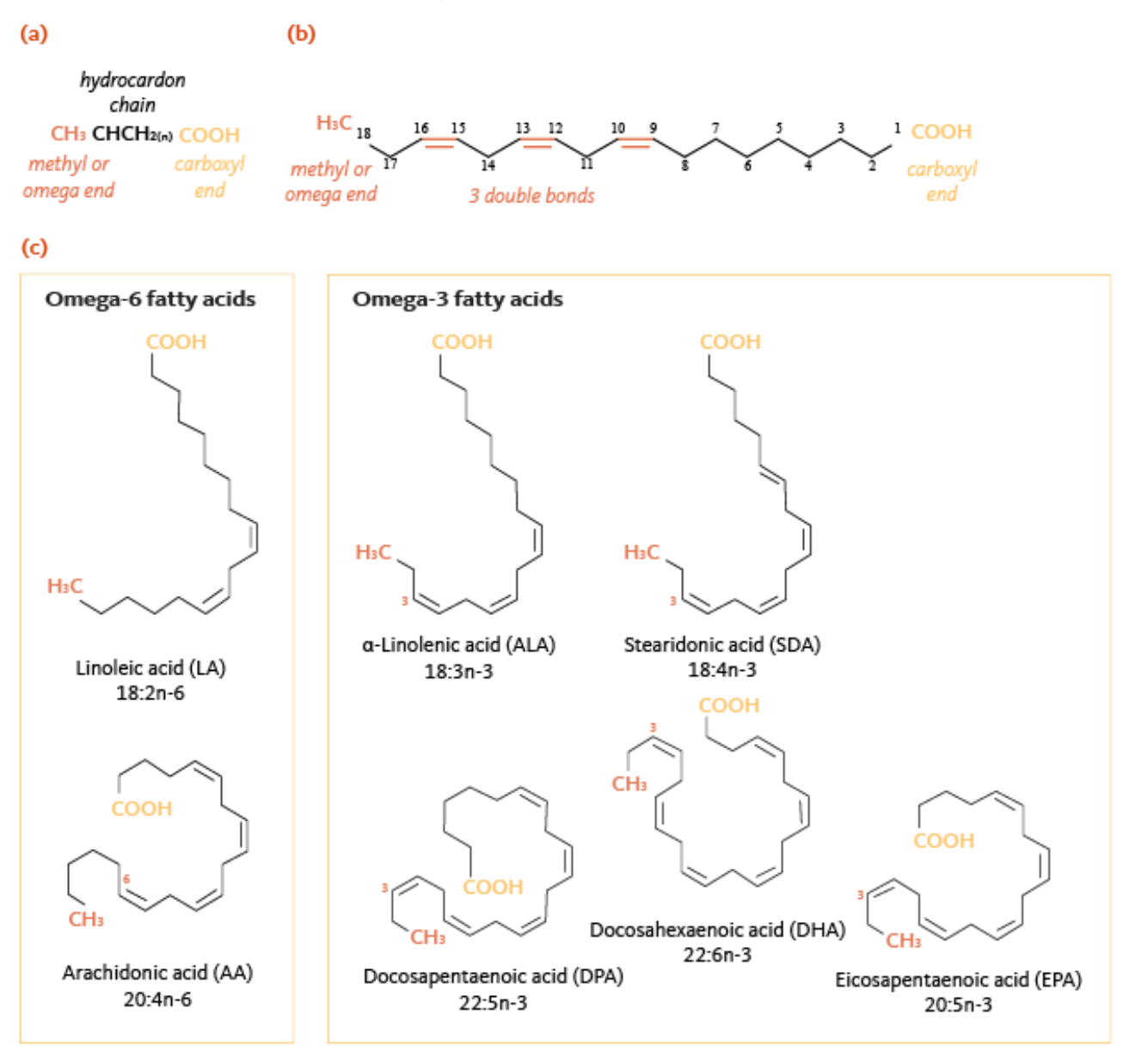
- Linoleic acid (LA), an omega-6 fatty acid, and α-linolenic acid (ALA), an omega-3 fatty acid, are considered essential fatty acids because they cannot be synthesized by humans. *(More information)*
- The long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can be synthesized from ALA, but due to low conversion efficiency, it is recommended to consume foods rich in EPA and DHA. *(More information)*
- Both omega-6 and omega-3 fatty acids are important structural components of cell membranes, serve as precursors to bioactive lipid mediators, and provide a source of energy. Long-chain omega-3 polyunsaturated fatty acids (PUFA in particular exert anti-inflammatory effects; it is recommended to increase their presence in the diet. *(More information)*
- Both dietary intake and endogenous metabolism influence whole body status of essential fatty acids. Genetic polymorphisms in fatty acid synthesizing enzymes can have a significant impact on fatty acid concentrations in the body. *(More information)*
- DHA supplementation during pregnancy may reduce the risks of early premature birth (birth before 34 weeks' gestation) and very low birth weight (<1.5 kg [<3 pounds 5 ounces]). *(More information)*
- DHA is important for visual and neurological development. However, supplementation with long-chain during pregnancy or early infancy appears to have no significant effect on children's visual acuity, neurodevelopment, and physical growth. *(More information)*
- Replacing saturated fat in the diet with omega-6 lowers total blood cholesterol; yet, randomized controlled trials have failed to demonstrate cardiovascular benefits in healthy people and people at risk for or with type 2 diabetes mellitus. Long-chain omega-3 PUFA supplementation may be useful to reduce mortality in patients with prevalent coronary heart disease (CHD) and in those with heart failure without preserved ventricular function. *(More information)*
- Increasing EPA and DHA intake may benefit individuals with type 2 diabetes mellitus, especially those with elevated serum triglycerides. However, evidence from large-scale randomized trials is insufficient to support the use of omega-3 PUFA supplements for cardiovascular disease prevention in those with type 2 diabetes. *(More information)*
- Observational studies have found fish intake to be associated with lower risks of cognitive deterioration and Alzheimer's disease, but it is not yet clear whether supplementation with marine-derived omega-3 PUFA can help prevent cognitive decline. *(More information)*
- Several omega-3 formulations have been approved by the US Food and Drug Administration for the indication of treating severe hypertriglyceridemia. *(More information)*
- Although omega-3 PUFA deficiency may not be uncommon in neurodevelopmental and neuropsychiatric disorders, there is little evidence to suggest that supplementation may be a beneficial adjunct in the management of affected individuals. *(More information)*
- The Food and Nutrition Board of the US Institute of Medicine (now the National Academy of Medicine) established adequate intakes (AI) for omega-6 and omega-3 fatty acids. *(More information)*

Introduction

Omega-6 and omega-3 fatty acids are polyunsaturated fatty acids (PUFA), meaning they contain more than one *cis* double bond (1). In all omega-6 (ω6 or n-6) fatty acids, the first double bond is located between the sixth and seventh carbon atom from the methyl end of the fatty acid. Likewise, all omega-3 fatty acids (ω3 or n-3) have at least one double bond between the third and fourth carbon atom counting from the methyl end of the fatty acid. Scientific abbreviations for fatty acids tell the reader something about their chemical structure. For example, the scientific abbreviation for α-linolenic acid (ALA) is 18:3n-3. The first part (18:3) tells the reader that ALA is an 18-carbon fatty acid with three double bonds, while the second part (n-3) tells the reader that the first double bond is in the n-3 position, which defines this fatty acid as an omega-3 (**Figures 1a & b**). Double bonds introduce kinks in the hydrocarbon chain that influence the structure and physical properties of the fatty acid molecule (**Figure 1c**).

Although humans and other mammals can synthesize saturated fatty acids and some monounsaturated fatty acids from carbon groups in carbohydrates and proteins, they lack the delta (Δ) 12 and Δ15 desaturase enzymes necessary to insert a *cis* double bond at the n-6 or the n-3 position of a fatty acid (1). Consequently, omega-6 and omega-3 fatty acids are essential nutrients. The parent fatty acid of the omega-6 series is linoleic acid (LA; 18:2n-6), and the parent fatty acid of the omega-3 series is ALA (**Figure 2** and **Table 1**). Humans can synthesize long-chain (20 carbons or more) omega-6 fatty acids, such as dihomo-γ-linolenic acid (DGLA; 20:3n-6) and arachidonic acid (AA; 20:4n-6), from LA and long-chain omega-3 fatty acids, such as eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), from ALA (see Metabolism and Bioavailability).

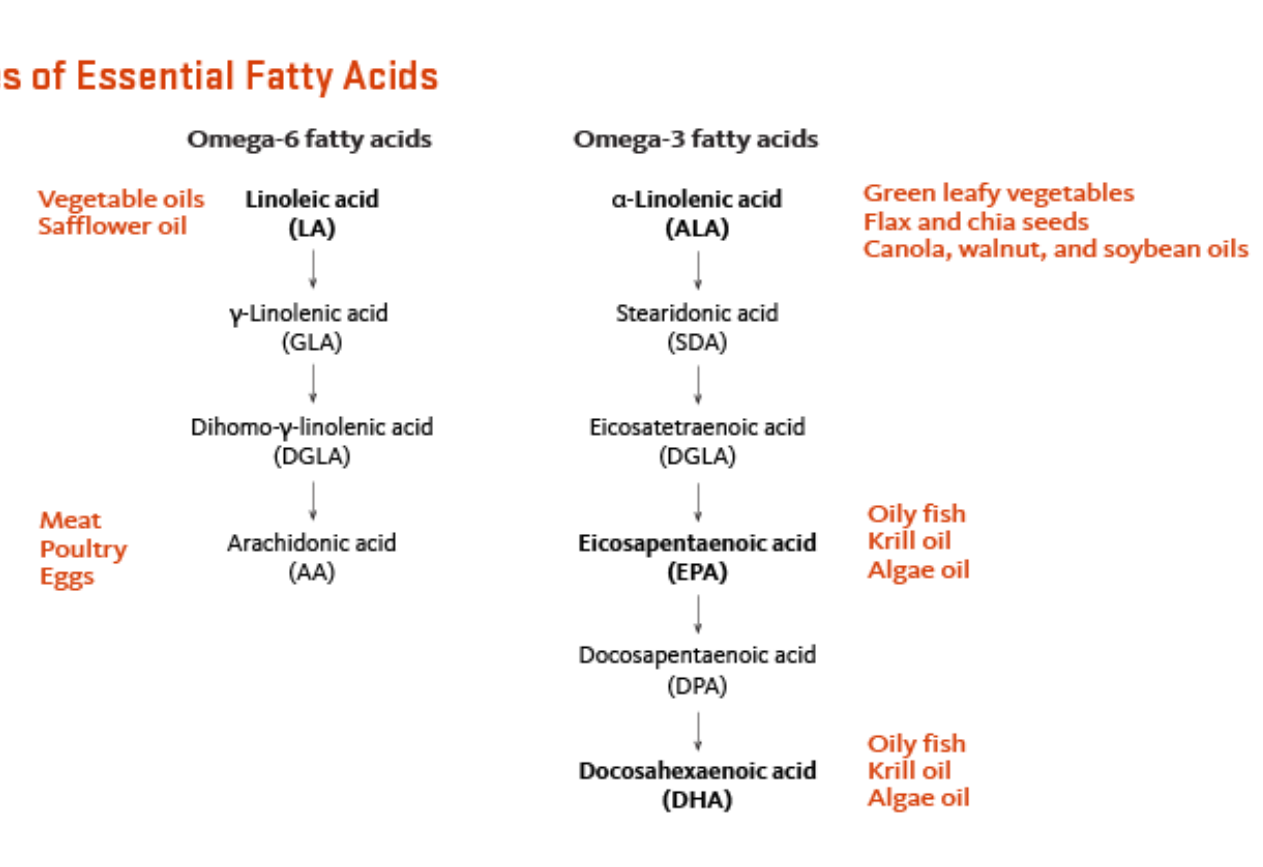
Figure 1. Chemical Structures of Fatty Acids



(a) The general structure of a fatty acid (22). (b) The chemical structure of α -linolenic acid (ALA), 18:3n-3. ALA has 18 carbon atoms (c) and 3 double bonds, the first of which is located 3 carbon atoms from the terminal methyl group (omega [ω] end). (c) The molecular structures of dietary omega-6 and omega-3 fatty acids. The presence of a double bond in the hydrocarbon chain of polyunsaturated fatty acids (PUFA) introduces a "kink" in the molecule, creating different secondary structures that influence physical properties (5).

[Figure 1a and 1b - Click to Enlarge] [Figure 1c - Click to Enlarge]

Figure 2. Classes of Essential Fatty Acids



Omega-6 (n-6) and omega-3 (n-3) fatty acids comprise the two classes of essential fatty acids (EFA). The parent compounds of each class, linoleic acid (LA) and α-linolenic acid (ALA) (bold font), give rise to longer chain derivatives inside the body. Due to low efficiency of conversion of ALA to the long-chain omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), it is recommended to obtain EPA and DHA from additional sources. Dietary sources of the different long-chain PUFA are listed in the colored boxes (25).

[Figure 2 - Click to Enlarge]

Table 1. Names and Abbreviations of the Omega-6 and Omega-3 Fatty Acids

Omega-6 Fatty Acids			Omega-3 Fatty Acids		
Linoleic acid	LA	18:2n-6	α-Linolenic acid	ALA	18:3n-3
γ-Linolenic acid	GLA	18:3n-6	Stearidonic acid	SDA	18:4n-3
Dihomo-γ-linolenic acid	DGLA	20:3n-6	Eicosatetraenoic acid	ETA	20:4n-3
Arachidonic acid	AA	20:4n-6	Eicosapentaenoic acid	EPA	20:5n-3
Adrenic acid		22:4n-6	Docosapentaenoic acid	DPA (n-3)	22:5n-3
Tetracosatetraenoic acid		24:4n-6	Tetracosapentaenoic acid		24:5n-3
Tetracosapentaenoic acid		24:5n-6	Tetracosahexaenoic acid		24:6n-3
Docosapentaenoic acid	DPA (n-6)	22:5n-6	Docosahexaenoic acid	DHA	22:6n-3

Metabolism and Bioavailability

Prior to absorption in the small intestine, fatty acids must be hydrolyzed from dietary fats (triglycerides and phospholipids) by pancreatic enzymes (2). Bile salts must also be present in the small intestine to allow for the incorporation of fatty acids and other fat digestion products into mixed micelles. Fat absorption from mixed micelles occurs throughout the small intestine and is small intestine to allow for the incorporation of fatty acids and other fat digestion products into mixed micelles. Fat absorption from mixed micelles occurs throughout the small intestine and is 85%-95% efficient under normal conditions.

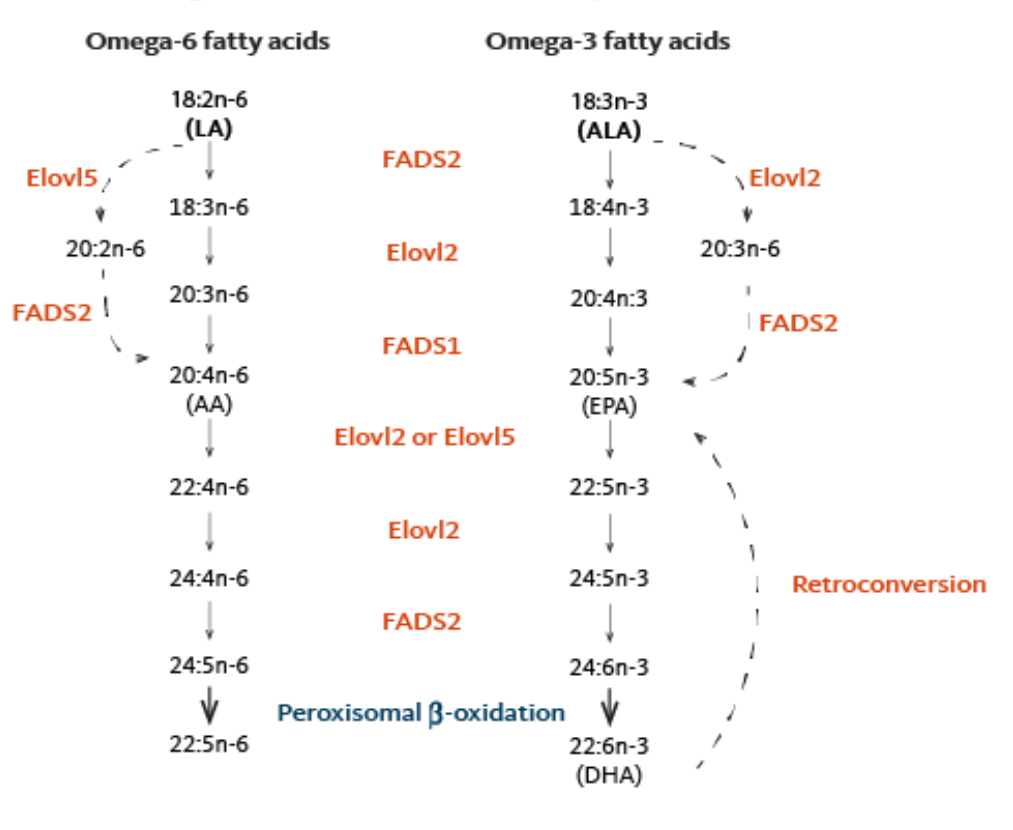
Concentrations of fatty acids in blood (i.e., whole blood, plasma, serum, and red blood cells) reflect both dietary intake and biological processes (3). Humans can synthesize longer omega-6 and omega-3 fatty acids from the essential fatty acids linoleic acid (LA) and α-linolenic acid (ALA), respectively, through a series of desaturation (addition of a double bond between two carbon atoms) and elongation (addition of two carbon atoms) reactions (**Figure 3**) (4, 5). LA and ALA compete for the same elongase and desaturase enzymes in the synthesis of longer polyunsaturated fatty acids (PUFA), such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

Studies of ALA metabolism in healthy young men indicated that approximately 8% of dietary ALA was converted to EPA and 0%-4% was converted to docosahexaenoic acid (DHA) (6). In healthy young women, approximately 21% of dietary ALA was converted to EPA and 9% was converted to DHA (7). The better capacity to generate long-chain PUFA from ALA in young women compared to men is related to the effects of estrogen (8, 9). Although only the essentiality of ALA is recognized because it cannot be synthesized *de novo* by humans, the relatively low rate of ALA conversion into EPA and DHA suggests that these long-chain omega-3 PUFA may be considered conditionally essential nutrients.

In addition to gender differences, genetic variability in enzymes involved in fatty acid metabolism influences one's ability to generate long-chain PUFA. Two key enzymes in fatty acid metabolism are delta 6 desaturase (FADS2) and delta 5 desaturase (FADS1) (**Figure 3**) (10). Two common haplotypes (a cluster of polymorphisms) in the FADS genes differ dramatically in their ability to generate long-chain PUFA: haplotype D is associated with increased FADS activity (both FADS1 and FADS2) and higher conversion rate of fatty acid precursors (LA and ALA) to long-chain PUFA (EPA, GLA, DHA, and AA) (11). These FADS polymorphisms are relatively common in the population and may explain up to 30% of the variability in blood concentrations of omega-3 and omega-6 fatty acids among individuals (3).

Finally, DHA can be retro-converted to EPA and DPA at a low basal rate and following supplementation (**Figure 3**) (12). After supplementing omnivores (n=8) and vegetarians (n=12) for six weeks with an EPA-free preparation of DHA (1.62 g/day), EPA, DPA, and DHA concentrations increased in serum and platelet phospholipids (13). Based on the measured changes, the estimated percent retroconversion of DHA to EPA was 7.4%-11.4% (based on serum phospholipid data) and 12.3%-13.8% (based on platelet phospholipid data), with no significant difference between omnivores and vegetarians. Due to this nontrivial retroconversion efficiency, DHA supplementation may represent an alternative to fish oil to increase blood and tissue concentrations of EPA, DPA, and DHA (see Supplements) (5).

Figure 3. Desaturation and Elongation of Essential Fatty Acids



Humans can synthesize longer omega-6 and omega-3 fatty acids from the essential fatty acids LA and ALA through a series of desaturation (addition of a double bond) and elongation (addition of two carbon atoms) reactions that occur in microsomes. Delta-6 desaturase (FADS2) is considered the rate-limiting enzyme in this metabolic pathway. Retroconversion of DHA to EPA in peroxisomes occurs at low basal rates and following DHA supplementation (4, 5). *FADS2, delta-6 desaturase; FADS1, delta-5 desaturase; Elovl2, Elovl5, elongases.*

[Figure 3 - Click to Enlarge]

Biological Activities

Membrane structure and function

Omega-6 and omega-3 PUFA are important structural components of cell membranes. When incorporated into phospholipids, they affect cell membrane properties, such as fluidity, flexibility, permeability, and the activity of membrane-bound enzymes and cell-signaling pathways (14, 15). In addition to endogenous metabolism, dietary consumption of fatty acids can modify the composition and molecular structure of cellular membranes. Thus, increasing omega-3 fatty acid intake increases the omega-3 content of red blood cells, immune cells (16), atherosclerotic plaques (17), cardiac tissue (18), and other cell types throughout the body.

DHA is selectively incorporated into retinal cell membranes and postsynaptic neuronal cell membranes, suggesting it plays important roles in vision and nervous system function. In fact, DHA represents the predominant PUFA in the retina and neuronal cells (19).

Vision

DHA is found at very high concentrations in the cell membranes of the retina; the retina conserves and recycles DHA even when omega-3 fatty acid intake is low (20). Animal studies indicate that DHA is required for the normal development and function of the retina. Moreover, these studies suggest that there is a critical period during retinal development when inadequate DHA will result in permanent abnormalities in retinal function. Research indicates that DHA plays an important role in the regeneration of the visual pigment rhodopsin, which plays a critical role in the visual transduction system that converts light hitting the retina to visual images in the brain (21).

Nervous system

The phospholipids of the brain's gray matter contain high proportions of long-chain PUFA, suggesting they are important to central nervous system function (22). AA stimulates glucose uptake by cortical astrocytes, meaning that it is important for energy metabolism (23). AA and DHA also increase the release of acetylcholine, which enhances synaptic plasticity and memory, thereby improving learning abilities (24). Although trials of PUFA supplementation during pregnancy and/or early infancy failed to show cognitive improvements in offspring (see Disease Prevention), the availability of omega-3 and omega-6 fatty acids to the fetus and infants is essential for the growth of their brain and development of brain functions. There is compelling evidence to suggest that PUFA are essential to neuronal growth and synapse formation, and for appropriate neurotransmission (reviewed in 25).

Synthesis of lipid mediators

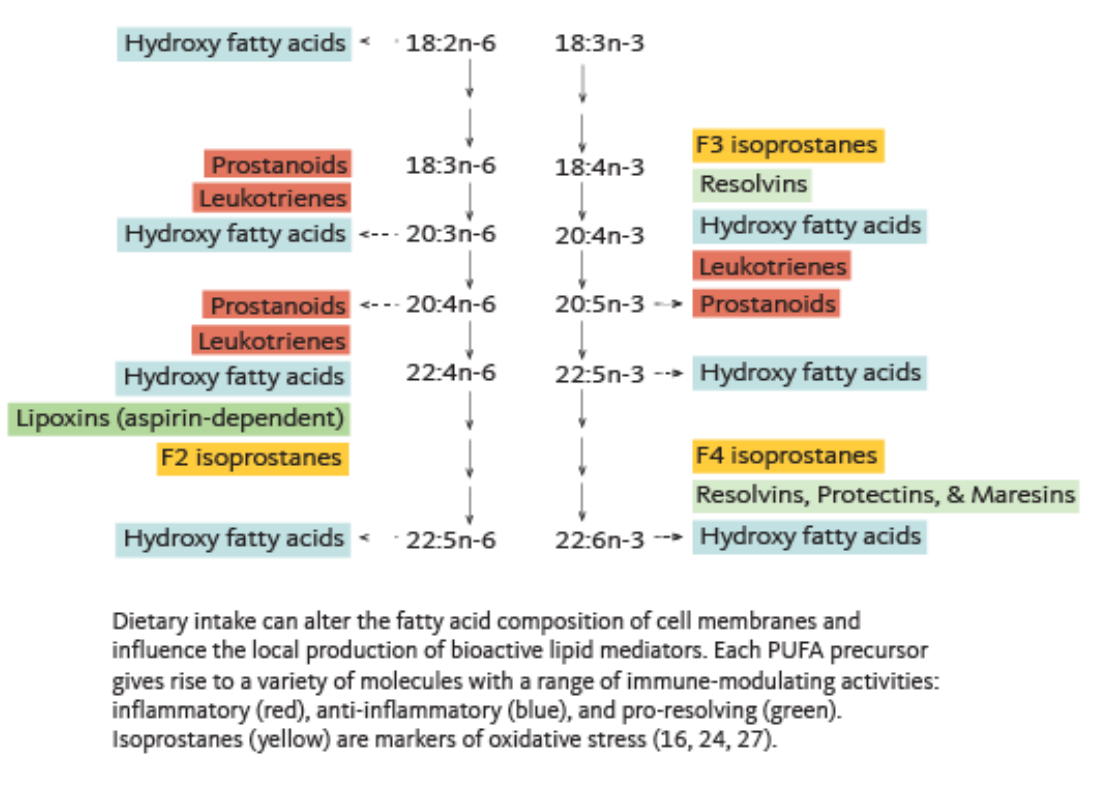
Oxylipins

Oxylipins are potent chemical messengers derived from PUFA. They play critical roles in immune and inflammatory responses. The most common oxylipins are eicosanoids that encompass numerous bioactive lipid mediators derived from 20-carbon ("eicosa-") AA. Following stimulation by hormones, cytokines, and other stimuli, PUFA bound to membrane phospholipids are released from cell membranes and become substrates for dodecanoid, eicosanoid, and docosanoid production. Oxylipin synthesis relies primarily on three families of enzymes: cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome p450 mono-oxygenases (P450s) (26). From C_{18}-C_{22} precursors, COX enzymes produce prostaglandins, prostacyclins, and thromboxanes (collectively known as prostanoids); LOX produces leukotrienes and hydroxy fatty acids; and P450s produce hydroxyeicosatetraenoic acids ("HETEs") and epoxides (**Figure 4**).

Physiological responses to AA-derived eicosanoids differ from responses to EPA-derived eicosanoids. In general, EPA is a poor substrate for eicosanoid production and EPA-derives eicosanoids are less potent inducers of inflammation, blood vessel constriction, and coagulation than eicosanoids derived from AA (19, 27).

Nonetheless, it is an oversimplification to label all AA-derived eicosanoids as pro-inflammatory. AA-derived prostaglandins induce inflammation but also inhibit pro-inflammatory leukotrienes and cytokines and induce anti-inflammatory lipoxins, thereby modulating the intensity and duration of the inflammatory response via negative feedback (**Figure 4**) (17).

Figure 4. Bioactive Lipid Mediators Derived from Omega-6 and Omega-3 Fatty Acids



Dietary intake can alter the fatty acid composition of cell membranes and influence the local production of bioactive lipid mediators. Each PUFA precursor gives rise to a variety of molecules with a range of immune-modulating activities: inflammatory (red), anti-inflammatory (blue), and pro-resolving (green). Isoprostanes (yellow) are markers of oxidative stress (16, 24, 27).

[Figure 4 - Click to Enlarge]

Pro-resolving mediators

A separate class of PUFA-derived bioactive lipids, specialized pro-resolving mediators (SPMs), has been more recently identified (reviewed in 28). These molecules function as local mediators of the resolution phase of inflammation, actively turning off the inflammatory response. SPMs are derived from both omega-6 and omega-3 PUFA (**Figure 4**) (29). The S-series of SPMs results from the LOX-mediated oxygenation of EPA and DHA, giving rise to S-resolvins, S-protectins, and S-maresins. A second class of SPMs, the R-series, is generated from the aspirin-dependent acetylation of COX-2 and subsequent generation of aspirin-triggered SPMs from AA, EPA, and DHA. It appears that these mediators may explain many of the anti-inflammatory actions of omega-3 fatty acids that have been described (16, 30).

Isoprostanes

Isoprostanes are prostaglandin-like compounds that are formed by non-enzymatic, free radical-induced oxidation of any PUFA with three or more double bonds (**Figure 4**) (26). Because they are produced upon exposure to free radicals, isoprostanes are often used as markers for oxidative stress. In contrast to prostanoids, isoprostanes are synthesized from esterified PUFA precursors and remain bound to the membrane phospholipid until cleaved by PLA_2 and released into circulation. In addition to being used as markers of oxidative stress, isoprostanes may also function as inflammatory mediators, exerting both pro- and anti-inflammatory effects (26).

Regulation of gene expression

PUFA are pleiotropic regulators of cell function. They can regulate gene expression directly by interacting with transcription factors or indirectly by influencing membrane lipid composition and cell signaling pathways.

The results of cell culture and animal studies indicate that omega-6 and omega-3 fatty acids can modulate the expression of a number of genes, including those involved with fatty acid metabolism and inflammation (31, 32). Omega-6 and omega-3 fatty acids regulate gene expression by interacting with specific transcription factors, such as peroxisome proliferator-activated receptors (PPARs) (33). In many cases, PUFA act like hydrophobic hormones (e.g., steroid hormones) to control gene expression and bind directly to receptors like PPARs. These ligand-activated receptors then bind to the promoters of genes and function to increase/decrease transcription.

In other cases, PUFA regulate the abundance of transcription factors inside the cell's nucleus (14). Two examples include NFϰB and SREBP-1. NFϰB is a transcription factor involved in regulating the expression of multiple genes involved in inflammation. Omega-3 PUFA suppress NFϰB nuclear content, thus inhibiting the production of inflammatory eicosanoids and cytokines. SREBP-1 is a major transcription factor controlling fatty acid synthesis, both *de novo* lipogenesis and PUFA synthesis. Dietary PUFA can suppress SREBP-1, which decreases the expression of enzymes involved in fatty acid synthesis and PUFA synthesis. In this way, dietary PUFA function as feedback inhibitors of all fatty acid synthesis.

By altering cell membrane fluidity, fatty acids can interfere with the activity of membrane receptor systems and thus indirectly influence signaling pathways and gene expression (34).

Deficiency

Essential fatty acid deficiency

Clinical signs of essential fatty acid deficiency include a dry scaly rash, decreased growth in infants and children, increased susceptibility to infection, and poor wound healing (35). Omega-3, omega-6, and omega-9 fatty acids compete for the same desaturase enzymes. The desaturase enzymes show preference for the different series of fatty acids in the following order: omega-3 > omega-6 > omega-9. Consequently, synthesis of the omega-9 fatty acid eicosatrienoic acid (20:3n-9, mead acid, or 5,8,11-eicosatrienoic acid) increases only when dietary intakes of omega-3 and omega-6 fatty acids are very low; therefore, mead acid is one marker of essential fatty acid deficiency (36). A plasma eicosatrienoic acid:arachidonic acid (triene:tetraene) ratio greater than 0.2 is generally considered indicative of essential fatty acid deficiency (35, 37). In patients who were given total parenteral nutrition containing fat-free, glucose-amino acid mixtures, biochemical signs of essential fatty acid deficiency developed in as little as 7 to 10 days (38). In these cases, the continuous glucose infusion resulted in high circulating insulin concentrations, which inhibited the release of essential fatty acids stored in adipose tissue. When glucose-free amino acid solutions were used, parenteral nutrition up to 14 days did not result in biochemical signs of essential fatty acid deficiency. Essential fatty acid deficiency has also been found to occur in patients with chronic fat malabsorption (39) and in patients with cystic fibrosis (40). It has been proposed that essential fatty acid deficiency may play a role in the pathology of protein-energy malnutrition (36).

Omega-3 fatty acid deficiency

At least one case of isolated omega-3 fatty acid deficiency has been reported. A young girl who received intravenous lipid emulsions with very little ALA developed visual problems and sensory neuropathy; these conditions were resolved when she was administered an emulsion containing more ALA (41). Isolated omega-3 fatty acid deficiency does not result in increased plasma triene:tetraene ratios, and skin atrophy and dermatitis are absent (1). Plasma DHA concentrations decrease when omega-3 fatty acid intake is insufficient, but no accepted plasma omega-3 fatty acid or eicosanoid concentrations indicative of impaired health status have been defined (1). Studies in rodents have revealed significant impairment of n-3 PUFA deficiency on learning and memory (42, 43), prompting research in humans to assess the impact of omega-3 PUFA on cognitive development and cognitive decline (see Cognitive and visual development and Alzheimer's disease).

Omega-3 index

The omega-3 index is defined as the amount of EPA plus DHA in red blood cell membranes expressed as the percent of total red blood cell membrane fatty acids (44). The EPA + DHA content of red blood cell membranes correlates with that of cardiac muscle cells (45, 46), and several observational studies indicate that a lower omega-3 index is associated with an increased risk of coronary heart disease mortality (47). It is therefore proposed that the omega-3 index be used as a biomarker for cardiovascular disease risk, with suggested cutoffs as follows: high risk, <4%; intermediate risk, 4%-8%; and low risk, >8% (48).

Supplementation with EPA + DHA from fish oil capsules for approximately five months dose-dependently increased the omega-3 index in 115 healthy, young adults (ages, 20-45 years), validating the use of the omega-3 index as a biomarker of EPA + DHA intake (49). Before the omega-3 index can be used in routine clinical evaluation, however, clinical reference values in the population must be established (50). Additionally, fatty acid metabolism may be altered in certain disease states, potentially making the omega-3 index less relevant for some cardiovascular conditions (5).

Disease Prevention

Pregnancy and early childhood developmental outcomes

Supplementation during pregnancy

Effect on pregnancy-associated conditions and neonatal outcomes: The results of randomized controlled trials during pregnancy suggest that omega-3 polyunsaturated fatty acid (PUFA) supplementation does not decrease the incidence of gestational diabetes and preeclampsia (51-54) but may result in modest increases in length of gestation, especially in women with low omega-3 fatty acid consumption. A 2006 meta-analysis of six randomized controlled trials in women with low-risk pregnancies found that omega-3 PUFA supplementation during pregnancy resulted in an increased length of pregnancy by 1.6 days (55). A 2007 meta-analysis of randomized controlled trials in women with high-risk pregnancies found that supplementation with long-chain PUFA did not affect pregnancy duration or the overall incidence of premature births (birth before 37 weeks' gestation) but decreased the incidence of early premature births (birth before 34 weeks' gestation; 2 trials, 291 participants) (56). Analyses of the secondary outcomes of the 2010 DHA to Optimize Mother-Infant Outcome (DOMInO) trial in 2,399 participants showed that supplementation with DHA-enriched fish oil capsules (800 mg/day of DHA and 100 mg/day of EPA) during pregnancy (from <21 gestational weeks until birth) reduced the risk of early premature birth but increased the risk of obstetrical interventions like the need for induction or cesarean section, when compared to supplementation with DHA-free vegetable oil capsules (57). A 2016 meta-analysis of trials found evidence to suggest that omega-3 PUFA supplementation during pregnancy reduced the overall risk of prematurity and the risk of early premature births, increased gestational age at delivery and birth weight, and had no effect on the risks of perinatal death and low Apgar scores at 1 minute post birth (58). A dose-response analysis found a continuous reduction of the risks of early premature birth (birth before 34 weeks' gestation) and very low birth weight (birth weight <1,500 g) with daily doses of DHA supplement up to at least 600 mg during pregnancy (59). There is currently limited evidence to support a role for omega-3 supplementation in the prevention of recurrent intrauterine growth restriction (IUGR) (60) or recurrent preterm birth (61).

Effect on children's cognitive and visual development: The effect of maternal omega-3 long-chain PUFA supplementation on early childhood cognitive and visual development was summarized in a 2013 systematic review and meta-analysis (62). Included in this assessment were 11 randomized controlled trials (a total of 5,272 participants) that supplemented maternal diet with omega-3 long-chain PUFA during pregnancy or both pregnancy and lactation. Results regarding visual outcomes (eight trials) could not be pooled together due to variability in assessments; overall, four of six trials had null findings and the remaining two trials had very high rates of attrition. Cognitive outcomes (nine trials) included the Developmental Standard Score (DSS; in infants, toddlers, and preschoolers) or Intelligence Quotient (IQ; in children) and other aspects of neurodevelopment, such as language, behavior, and motor function. No differences were found between DHA and control groups for cognition measured with standardized psychometric scales in infants (<12 months), toddlers (12-24 months), and school-aged children (5-12 years); preschool children (2-5 years) in the DHA treatment group had a substantially higher DSS score compared to controls. The authors noted that many of the trials of long-chain PUFA supplementation in pregnancy had methodological weaknesses (e.g., high rates of attrition, small sample sizes, high risk of bias, multiple comparisons), limiting the confidence and interpretation of the pooled results. Of note, a seven-year follow-up of the DOMInO trial is currently underway to assess the effect of DHA supplementation during pregnancy on child IQ and various measures of cognitive development (e.g., executive functioning, memory, language) (63).

Effect on children's body composition: The follow-up of 1,531 children whose mothers were randomized to supplemental DHA (800 mg/day) or a control during the second half of pregnancy in the DOMInO trial showed no effect of maternal DHA supplementation on the body mass index (BMI)-for-age z score and percentage of body fat of their children at three and five years of age (64). Measures of insulin resistance in 5-year-old children were unexpectedly higher in children whose mothers were in the DHA group than in those whose mothers were in the control group (64). Further analyses conducted in a subset of children (252) at age seven years again showed no effect of DHA supplementation on BMI z score, percentage of body fat, height, weight, and waist/hip circumference (65). Current evidence from 10 randomized controlled trials primarily conducted in high-income countries (all but one) suggests no influence of maternal supplementation with long-chain PUFA on the body composition and anthropometry of the offspring (66).

Effect on children's risk of allergies and asthma: A 2018 meta-analysis of randomized controlled trials in 2,047 children followed for six months to 16 years found a 19% lower risk of wheezing and/or asthma with maternal supplementation of omega-3 PUFA (primarily EPA and DHA) from as early as the 20th week of gestation until delivery (67). However, there was no effect of prenatal supplementation when the analysis was restricted to the three trials that reported on the incidence of childhood asthma only (67). Another meta-analysis of nine trials in 3,637 children, including three trials in which maternal supplementation with omega-3 PUFA continued after birth, found no effect of prenatal supplements on the risk of any allergy (three trials), the risk of wheeze and/or asthma (seven trials), the risk of eczema (six trials), the development of allergic rhinitis (two trials), and the risk of food allergy (three trials) in children (68). There was, however, some evidence to suggest that prenatal supplementation could lower the incidence of sensitization to specific allergens, namely egg (three trials; -46%) and peanut (two trials; -38%) (68).

Supplementation to breast-feeding mothers

A 2015 systematic review and meta-analysis summarized the results of eight randomized controlled trials that examined the effect of maternal supplementation with long-chain PUFA during either pregnancy and lactation or lactation only on the development and growth of their infants over the first two years of life and beyond (69). All studies were conducted in high-income countries. No differences between long-chain PUFA supplementation and control were observed in terms of language development, intelligence or problem-solving ability, psychomotor development, and anthropometric measurements (weight, length/height, head circumference, BMI, fat mass distribution) (69).

Supplementation in infants

The last trimester of pregnancy and first six months of postnatal life are critical periods for the accumulation of DHA in the brain and retina (70). Human milk contains a mixture of saturated fatty acids (~46%), monounsaturated fatty acids (~41%), omega-6 PUFA (~12%), and omega-3 PUFA (~1.3%) (71). Although human milk contains DHA in addition to ALA and EPA, ALA was the only omega-3 fatty acid present in conventional infant formulas until the year 2001. Although infants can synthesize DHA from ALA, they generally cannot synthesize enough to prevent declines in plasma and cellular DHA concentrations without additional dietary intake. Therefore, it was proposed that infant formulas be supplemented with enough DHA to bring plasma and cellular DHA concentrations of formula-fed infants up to those of breast-fed infants (72).

All infants: Although formulas enriched with DHA raise plasma and red blood cell DHA concentrations in preterm and term infants, the results of randomized controlled trials examining measures of visual acuity and neurological development in infants fed formula with or without added DHA have been mixed. For instance, a 2012 meta-analysis of randomized controlled trials (12 trials, 1,902 infants) comparing long-chain PUFA-supplemented and unsupplemented formula, started within one month of birth, found no effect of long-chain PUFA supplementation on infant cognition assessed at approximately one year of age (73). A lack of effect was observed regardless of the dose of long-chain PUFA or the prematurity status of the infant. With respect to visual acuity, a 2013 meta-analysis of randomized controlled trials (19 trials, 1,949 infants) found a beneficial effect of long-chain PUFA-supplemented formula, started within one month of birth, on infant visual acuity up to 12 months of age (74). Notably, two different types of visual acuity assessment were evaluated in the meta-analysis. Visual acuity assessed by using the Visually Evoked Potential (10 trials, 852 infants) showed a significant positive effect of long-chain PUFA-supplemented formula at 2, 4, and 12 months of age. When assessed by the Behavioral Method (12 trials, 1,095 infants), a significant benefit of long-chain PUFA-supplemented formula on visual acuity was found only at the age of two months. No moderating effects of dose or prematurity status were observed.

Preterm infants: A few trials have been specifically conducted in preterm infants. This is the case of the DHA for the Improvement of Neurodevelopmental Outcome (DINO) trial that initially enrolled 657 very preterm infants (born <33 gestational weeks) in five Australian hospitals (75). The aim of the trial was to examine the effect of enteral feeds with either high DHA (1% of total fatty acids) or standard DHA level (0.3% of total fatty acids) to preterm infants from age 2 to 4 days of life until term's corrected age (mean duration, 9.4 weeks) on their mental and psychomotor development, assessed at 18 months' and 7 years' corrected ages. At the 18-month follow-up, there was no difference in mean Mental Development Index (MDI) and Psychomotor Development Index (PDI) test scores between high-DHA and standard-DHA groups; yet, better MDI scores in girls fed high-DHA versus those fed standard-DHA feeds were reported in subgroup analyses (75). Post-hoc analyses also suggested fewer cases with delayed mental development among girls and infants weighing <1,250 kg at birth in the high- versus standard-DHA group (75). Follow-up at 7 years' corrected age showed no difference between groups in measures of IQ and cognitive development, including attention, short-term verbal memory and learning ability, executive functioning, visual perception, and academic achievement (76). A 2016 systematic review of 17 trials found little evidence to suggest that supplementing preterm infants with long-chain PUFA (primarily AA and DHA) improved measures of visual acuity, neurodevelopment, and physical growth during infancy (77).

Cardiovascular disease

Omega-6 fatty acids

Linoleic acid (LA) is the most abundant dietary PUFA and accounts for approximately 90% of dietary omega-6 PUFA intake (78).

Observational studies: A pooled analysis of 13 prospective cohort studies, encompassing 310,602 individuals and 12,479 coronary heart disease (CHD) events (of which resulted in 5,882 CHD deaths) over follow-up periods of 5.3 to 30 years, found higher LA intakes to be associated with a 15% lower risk of CHD events and a 21% lower risk of CHD mortality (79). A dose-response analysis found that replacing 5% of energy from saturated fatty acids with LA was associated with a 9% lower risk of coronary events and a 13% lower risk of coronary deaths (79). A 2019 meta-analysis of 30 prospective cohort studies in 68,659 participants found that individuals in the highest versus lowest quintile of LA concentrations in tissues (primarily blood compartments) had a 23% lower risk of cardiovascular mortality (80). No associations were found between LA concentrations in tissues and the risks of CHD, ischemic stroke, or total cardiovascular disease (80).

Randomized controlled trials: Taking into consideration the results from four randomized controlled trials (81-85) that compared the effects of diets either high in saturated fatty acids or PUFA over at least two years, a 2016 systematic review and presidential advisory from the American Heart Association concluded that lowering saturated fat intake and replacing it with vegetable oil rich in PUFA (primarily soybean oil) could reduce the risk of CHD by 29% (86). Of note, these trials were conducted in the 1960s and 1970s, when the use of cholesterol-lowering drug statin was not widespread and the saturated fat content in diets was higher; all but one trial (84, 85) were in men with diagnosed cardiovascular disease (CVD). Among these four trials, the Oslo Diet-Heart Study (83) increased both omega-3 and omega-6 PUFA intake, and the Finnish Mental Hospital Study (84, 85) used a cross-over design — both trials were excluded from a Cochrane systematic review of 19 randomized controlled trials that examined the effect of increasing omega-6 PUFA intake on CVD outcomes (87). Of these 19 trials, seven assessed the effect of supplemental γ-linolenic acid (GLA) and 12 assessed the effect of substituting dietary LA for saturated or monounsaturated fatty acids. The pooled analysis of studies showed no effect of increasing omega-6 intake on the risks of CHD or CVD events, major adverse cardiac and cerebrovascular events, myocardial infarction (MI), stroke, CVD mortality, or all-cause mortality (low-quality evidence) (87). Moreover, many trials that examined the effect of replacing saturated fatty acids with mostly omega-6 PUFA may not have been adequately controlled. For example, in some trials, only the experimental group (the high omega-6 PUFA group) received dietary advice regarding more than just replacing saturated fatty acids by omega-3 PUFA, e.g., to avoid dietary sources of *trans* fatty acids and processed foods, to consume more whole-plant foods, to lower sugar consumption, to increase consumption of fish and shellfish, which could have biased the results (88). Additionally, a recent meta-analysis of trials with low risk of bias (i.e., free of differences between intervention and control groups other than those under examination) showed no evidence of an effect of substituting omega-6 PUFA for saturated fatty acids on the risks of major CHD events (MI and sudden death), total CHD events, CHD mortality, and all-cause mortality (88).

Yet, replacing dietary saturated fatty acids with omega-6 PUFA was consistently found to lower total blood cholesterol concentrations (87, 89). In fact, LA has been shown to be the most potent fatty acid for lowering total cholesterol when substituted for dietary saturated fatty acids (90). The potential mechanisms by which LA reduces blood cholesterol include (1) the upregulation of LDL receptor and redistribution of LDL-cholesterol from plasma to tissue, (2) the increase in bile acid production and cholesterol catabolism, and (3) the decreased VLDL-to-LDL conversion (91). However, if substituting omega-6 PUFA for saturated fatty acids can reduce blood cholesterol, the most recent systematic reviews and meta-analyses have failed to find evidence of clinical cardiovascular benefits (see above) (87, 88, 92).

Omega-3 fatty acids

Observational studies: A meta-analysis of 17 prospective and two retrospective cohort studies in 45,637 generally healthy participants found that circulating concentrations of α-linolenic acid (ALA) and longer chain omega-3 PUFA (i.e., eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], docosahexaenoic acid [DHA]) were inversely associated with the risk of fatal coronary heart disease (CHD) (93).

Several observational studies also examined the relationship between dietary ALA intake and the risk of CHD. A 2018 meta-analysis of 14 prospective cohort studies in a total of 345,202 participants free of cardiovascular disease (CVD) evaluated the risk of composite CHD outcomes (combining different CHD events) and fatal CHD in relation to dietary consumption of ALA (94). Overall, the pooled analysis found a 9% lower risk of composite CHD outcomes and a 15% lower risk of fatal CHD with higher ALA exposure (94). Further, a number of prospective cohort studies have examined the consumption of fish, rich in long-chain omega-3 PUFA (mainly EPA and DHA), in relation to various cardiovascular events and mortality. A 2018 review of the evidence and advisory from the American Heart Association concluded that seafood intake was associated with modestly lower risks of CHD, ischemic stroke, and sudden cardiac death, and noted a greater benefit when intake went from zero to one or two seafood meals per week and when seafood was substituted for less healthy options like processed meat (95). In contrast, recently published meta-analyses of prospective cohort studies found little evidence of inverse associations between fish consumption and either CHD or stroke (96, 97). Higher fish consumption was found to be associated with lower risks of myocardial infarction (MI) (98) and congestive heart failure (96). In addition, one meta-analysis of 12 prospective cohort studies found a 6% lower risk of all-cause mortality with the highest versus lowest level of fish consumption (99). Yet, another meta-analysis found no association between fish intake and all-cause mortality but a 4% lower risk of CVD mortality for each 20-g/day increment in fish intake (100).

The potential cardiovascular benefit of seafood consumption appears to be tightly linked to the type of seafood (e.g., fatty or lean fish), the way it is prepared (e.g., baked, broiled, or fried), the presence of toxic metals and environmental contaminants, and the habitual level of consumption (high versus low) — these factors may be confounding the results reported in observational studies and pooled analyses (95). Although seafood is a good source of long-chain omega-3 PUFA, health benefits associated with fish consumption could be attributed to the presence of other nutritional factors (e.g., micronutrients and high-quality protein) and that seafood consumption is usually a marker of higher socioeconomic status, as well as healthy lifestyles (101, 102).

Randomized controlled trials: A 2018 Cochrane systematic review assessed the evidence for a cardioprotective effect of ALA and long-chain omega-3 PUFA in individuals either at low or high risk of CVD (103). Moderate-to-high quality evidence from randomized controlled trials (of at least 12 months) suggested no effect of omega-3 PUFA (either supplemented, enriched in meals, or advised to be consumed) on the risk of CHD events, CVD events, arrhythmia, stroke, CHD mortality, CVD mortality, or all-cause mortality. There was also no evidence of an effect on secondary outcomes, including major adverse cerebrovascular or cardiovascular events, MI, sudden cardiac death, angina pectoris, heart failure, revascularization, peripheral arterial disease, and acute coronary syndrome (103). A 2017 review and advisory from the American Heart Association found no evidence to suggest a benefit of long-chain omega-3 PUFA supplementation for the prevention of cardiovascular mortality in patients with or at risk of type 2 diabetes mellitus, the prevention of CHD in patients with atherosclerotic disease (e.g., with prior stroke, peripheral vascular disease, diabetes, hypercholesterolemia), the prevention of stroke in patients with or without a history of stroke, and the prevention of atrial fibrillation in patients with prior atrial fibrillation or in those undergoing cardiac surgery (104). There was some evidence to suggest that supplementation with long-chain omega-3 PUFA in patients with prior clinical CHD might reduce the risk of CHD death, possibly because of a reduction in the risk of ischemia-induced sudden cardiac death (104).

Hypertriglyceridemia (borderline high: serum triglycerides 150-199 mg/dL; high: serum triglycerides >200 mg/dL) is an independent risk factor for cardiovascular disease (105). Numerous controlled clinical trials have demonstrated that increasing intakes of EPA and DHA significantly lower serum triglyceride concentrations (103). The triglyceride-lowering effects of EPA and DHA increase with dose (106), but clinically meaningful reductions in serum triglyceride concentrations have been demonstrated at doses of 2 g/day of EPA + DHA (107). Although long-chain omega-3 PUFA can reduce triglyceride concentrations, they have no effect on total cholesterol, LDL-cholesterol, or HDL-cholesterol in blood (103). Of note, the mechanisms by which long-chain omega-3 PUFA supplements may reduce CHD death are unlikely to involve a lowering of triglycerides as doses used in the studies (~1 g/day) were generally too low (104). Some studies in cell culture indicated that long-chain omega-3 PUFA may decrease the excitability of cardiac muscle cells (myocytes) by modulating ion channel conductance, which would be consistent with anti-arrhythmic effects observed in animal models (see also Hypertriglyceridemia) (108, 109).

Summary

Replacing dietary saturated fatty acids with omega-6 PUFA lowers total blood cholesterol, yet there is no convincing evidence of an effect of omega-6 PUFA on the risk of major CVD events. Although evidence supports the adoption of a heart-healthy dietary pattern that includes two servings of seafood per week (95), supplementation with long-chain omega-3 fatty acids is unlikely to result in cardiovascular benefits in generally healthy people with a low CVD risk or in individuals at risk of or with type 2 diabetes mellitus (104). In its recommendations regarding omega-3 fatty acids and cardiovascular disease (see Intake Recommendations), the American Heart Association indicates that long-chain omega-3 PUFA supplementation may be useful to reduce mortality in patients with prevalent CHD (e.g., who suffered a recent MI) and in those with heart failure without preserved ventricular function (104).

Cardiometabolic risk factors in individuals with diabetes mellitus

Type 2 diabetes mellitus: Cardiovascular disease is the leading cause of death in individuals with diabetes mellitus. The dyslipidemia typically associated with diabetes is characterized by a combination of hypertriglyceridemia (serum triglycerides >200 mg/dL), low HDL-cholesterol, and abnormal LDL-cholesterol (110). Lipid-lowering therapy to normalize diabetic dyslipidemia and reduce cardiovascular risk includes lifestyle modification and medications — particularly the use of cholesterol-lowering statins (111, 112). Additionally, achieving glucose control in people with type 2 diabetes has been shown to decrease the occurrence of major microvascular and macrovascular events (113).

A 2014 meta-analysis of 19 randomized controlled trials, including 24,788 individuals with either impaired glucose metabolism or type 2 diabetes mellitus, found that long-chain omega-3 PUFA supplementation (doses, 360-10,000 mg/day; for 6 weeks to 6 years) lowered serum triglyceride concentrations by 0.25 mmol/L but had no substantial effect on total cholesterol, LDL-cholesterol, or HDL-cholesterol (114). There was also no significant effect on HbA1c, fasting glucose, blood pressure, heart rate, or a measure of endothelial function. Four trials that lasted over a year reported on cardiovascular outcomes, including mortality. The pooled analysis of these trials found no effect of supplementation with omega-3 PUFA on the risk of major cardiovascular events, cardiovascular mortality, all-cause mortality, or a composite endpoint of all-cause mortality and hospitalization for a cardiovascular cause. It is worth noting that two of these trials — the Alpha Omega Trial (115) and the ORIGIN trial (116) — included a high proportion of participants who took cardiovascular medications (i.e., cholesterol-lowering statins) (114). Another meta-analysis of 45 randomized controlled trials in 2,674 participants with type 2 diabetes found that supplementation with omega-3 (400-1,800 mg/day for 2 weeks to 2 years) led to small decreases in blood concentrations of triglycerides, VLDL-triglycerides, LDL-cholesterol, and vLDL-cholesterol (117). There was no evidence of an effect on total cholesterol, HDL-cholesterol, non-esterified fatty acids, apolipoprotein-A1, and apolipoprotein-B. There was a reduction in circulating concentrations of pro-inflammatory cytokines, TNF-α and IL-6, in response to omega-3 supplementation, yet not of C-reactive protein (CRP) — a marker of low-grade inflammation. Omega-3 PUFA supplementation had no effect on systolic or diastolic blood pressure. Finally, a small decrease in HbA1c was reported in response to supplemental omega-3 fatty acids, yet there was no effect on other indicators of glycemic control, especially fasting glucose, fasting insulin, connecting (C-) peptide, and a measure of insulin resistance (117).

Lifestyle changes involving dietary modifications, such as the substitution of healthy fats (mono- and poly-unsaturated fatty acids) for saturated and *trans* fats, are recommended to reduce the risk of cardiovascular disease in people with type 2 diabetes mellitus (118). In their most recent updated recommendations on the prevention of cardiovascular disease in adults with type 2 diabetes, the American Diabetes Association and American Heart Association found insufficient evidence from large-scale randomized trials in individuals with type 2 diabetes to support the use of omega-3 fatty acid supplements (combined with a heart-healthy diet) in the prevention of cardiovascular events (118).

Gestational diabetes: Poor glycemic control during pregnancy, whether due to type 1 diabetes, type 2 diabetes, or gestational diabetes, increases the risk of fetal anomalies, preeclampsia, spontaneous abortion, stillbirth, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia (119). Diabetes during pregnancy is also associated with a higher risk of metabolic disorders in offspring later in life (119). A team of investigators in Iran examined the effect of omega-3 PUFA supplementation during pregnancy, beginning at 24 to 28 weeks' gestation for six weeks, in women with gestational diabetes. Overall, there was evidence of beneficial effects of 1,000 mg/day of omega-3 alone (120) or together with vitamin E (121) or vitamin D (122) on markers of glucose homeostasis and, to a lesser extent, on markers of oxidative stress and inflammation and blood lipid profile. In one randomized, placebo-controlled trial in 60 women with gestational diabetes, supplementation with omega-3 fatty acids and vitamin E reduced the risk of neonatal hyperbilirubinemia yet had no effect on the rate of cesarean section, need for insulin therapy, maternal hospitalization, newborns' hospitalization, gestational age, birth size, and Apgar score (122).

Current recommendations by the American Diabetes Association for the management of gestational diabetes encourage the development of an individualized nutrition plan between a woman and a registered dietitian, highlighting the importance of the amount and type of carbohydrates in the diet (119). The use of omega-3 supplements in the management of gestational diabetes is not currently under consideration.

Type 2 diabetes mellitus

A meta-analysis of 13 randomized, controlled feeding trials that substituted plant-derived PUFA (primarily linoleic acid [LA]) for saturated fatty acids or carbohydrates for 3 to 16 weeks in generally healthy adults showed a decrease in fasting insulin concentration and insulin resistance but no effect on fasting glucose concentration (123). Most studies used a mixture of omega-3 and omega-6 PUFA in the form of plant-derived oils such that potential differences in effect between them could not be examined.

A meta-analysis of 20 prospective cohort studies conducted in 10 countries, in a total of 39,740 participants free from diabetes at baseline, examined biomarkers of omega-6 intake in relation to the risk of developing type 2 diabetes mellitus (124). LA ranged from 8.3% of total fatty acids in erythrocyte phospholipids to 54.5% in plasma cholesterol esters. The lowest percentage of arachidonic acid (AA) was found in adipose tissue (0.3%) and the highest in erythrocyte phospholipids (17.0%). The highest versus lowest concentration of LA markers in each compartment (phospholipids, plasma or serum, cholesterol esters) except adipose tissue was associated with a 35% lower risk of type 2 diabetes. In contrast, only AA in plasma or serum was inversely associated with the risk of type 2 diabetes (124). If LA concentration in blood and adipose tissue can provide an objective assessment of dietary LA intake (125), these results suggest that dietary LA may be important for glycemic control and diabetes prevention.

Metabolic syndrome

A 2019 meta-analysis of 13 observational (9 cross-sectional, 2 case-control, 1 nested case-control, and 1 prospective cohort; 36,542 participants) studies showed higher concentrations of omega-3 in blood and adipose tissue and higher level of omega-3 intake to be associated with a lower risk of metabolic syndrome (126). No association was found between tissue omega-6 concentration or dietary omega-6 intake level and the risk of metabolic syndrome (126).

Cognitive decline and Alzheimer's disease

Alzheimer's disease is the most common cause of dementia in older adults (127). Alzheimer's disease is characterized by the formation of amyloid plaque in the brain and nerve cell degeneration. Disease symptoms, including memory loss and confusion, worsen over time (128).

Observational studies: Several observational studies have examined dietary fish and PUFA consumption in relation to risks of cognitive decline, dementia, and Alzheimer's disease. The pooled analysis of five large prospective cohort studies (Three-City Study, Nurses' Health Study, Women's Health Study, Chicago Health and Aging Project, and Rush Memory and Aging Project) that followed a total of 23,688 older (ages, ≥65 years) participants (88% women) for 3.9 to 9.1 years found slower rates of decline in episodic memory and global cognition with increasing fish intakes (129). Previous studies have suggested that the effect of fish or PUFA consumption on cognition may be dependent on apolipoprotein E (APOE) genotype (130, 131). Of three common APOE alleles (epsilon 2 [ε2], ε3, and ε4), the presence of the APOE ε4 (E4) allele has been associated with increased risk and earlier onset of Alzheimer's disease (132). It was found that long-chain omega-3 PUFA supplementation did not increase plasma omega-3 concentrations to the same extent in E4 carriers than in non-carriers (133) and that DHA metabolism differs in E4 carriers compared to non-carriers, with greater oxidation and lower plasma concentrations in E4 carriers (134). However, neither APOE genotype nor polymorphisms in 11 other genes associated with Alzheimer's disease were found to modify the inverse relationship between fish intake and risk of cognitive decline in the pooled analysis of the five cohorts (129).

In a recent meta-analysis of observational studies, each one-serving increase of fish intake per week was found to be associated with a 5% lower risk of dementia and a 7% lower risk of Alzheimer's disease (135). Dietary intake level of marine-derived DHA — but not blood DHA concentration — was also inversely associated with the risks of dementia and Alzheimer's disease; for instance, a 100 mg/day increment in dietary DHA intake was associated with lower risks of dementia (-14%) and Alzheimer's disease (-37%) (135). Results from two large cohort studies published after this dose-response meta-analysis showed blood DHA concentration to be positively associated with cognitive performance in adults (136, 137). Findings from preclinical studies suggest that long-chain omega-3 fatty acids may have neuroprotective effects, potentially through mitigating neuroinflammation, improving cerebral blood flow, and/or reducing amyloid aggregation (138).

Randomized controlled trials: A 2012 systematic review identified three randomized controlled trials that examined the effect of omega-3 supplementation on the risk of cognitive decline in cognitively healthy older or elderly adults (139). There was no evidence showing an effect of omega-3 on measures of cognitive functions in these clinical trials. In a more recent systematic review that identified seven trials conducted in cognitively healthy participants, the authors reported positive effects of long-chain omega-3 supplementation on measures of cognitive outcomes in all studies but the second longest and the two largest trials (140). Another seven trials examined the effect of long-chain omega-3 supplementation in individuals with mild cognitive impairment; all but three trials showed a significant benefit on measures of cognitive function or specific memory tasks (140). Yet, two trials that found no improvement in cognitive performance included omega-3 supplements in both intervention and control arms (141, 142).

Overall, the data favor a role for diets rich in long-chain omega-3 fatty acids in slowing cognitive decline, but larger trials with longer intervention periods may be necessary to see a consistent beneficial effect of omega-3 supplementation in older individuals with normal or declining cognitive functions.

Disease Treatment

Hypertriglyceridemia

About one-third of US adults have serum triglycerides >150 mg/dL, and 16% of US adults have serum triglycerides >200 mg/dL (143). The 2011 American Heart Association guidelines on triglyceride management recommended the use of marine-derived omega-3 fatty acid supplements (2-4 g/day of EPA plus DHA) under medical supervision to reduce triglyceride concentrations below 100 mg/dL (143). Hypertriglyceridemia can have various causes, such as inherited and acquired disorders of triglyceride metabolism, poor diet, and/or use of certain medications (143).

Several omega-3 fatty acid preparations have been approved by the US Food and Drug Administration for the treatment of hypertriglyceridemia (104). Out of the five currently available preparations, four contain ethyl esters of EPA and/or DHA and one contains long-chain omega-3 PUFA as free fatty acids (104). The Epanova for lowering very high triglycerides (EVOLVE) randomized controlled trial demonstrated that the omega-3 free fatty acid formulation (2-4 g/day for 12 weeks) effectively reduced triglycerides and other atherogenic factors, including vLDL-cholesterol and remnant-like cholesterol particles, when compared to olive oil (4 g/day) in patients with severe hypertriglyceridemia (serum triglycerides >500 mg/dL) (reviewed in 144). Omega-3 supplementation also decreased inflammation (as shown by a reduction in lipoprotein-associated phospholipase A2) and platelet activation (as shown by a reduction in circulating concentrations of arachidonic acid) (144, 145). This omega-3 formulation also proved to be effective in reducing persistent hypertriglyceridemia (serum triglycerides, 200-499 mg/dL) in patients treated with statins (cholesterol-lowering drugs) (146). Statin use has been found to effectively reduce triglyceride concentrations by about 5%-20% (147). However, a residual elevation in triglycerides and triglyceride-rich lipoprotein cholesterol may remain in a substantial fraction of patients treated with statins. Compared to 4 g/day of olive oil, omega-3 supplementation with 2 or 4 g/day for six weeks reduced triglycerides by 14.6% and 20.6% and non-HDL-cholesterol by 3.9% and 6.9%, respectively (146). The magnitude of these reductions in triglyceride and non-HDL-cholesterol concentrations was similar to what has been observed in other trials that examined the use of ethyl ester omega-3 supplements as add-ons to statin therapy (146, 148-150). A study is underway to assess the benefit of combining omega-3 fatty acids and statins on the risk of major cardiovascular events over a three- to five-year period in patients with hypertriglyceridemia (144, 151).

Nonalcoholic fatty liver disease

Often associated with metabolic disorders, nonalcoholic fatty liver disease (NAFLD) is a condition characterized by an excessive lipid accumulation in the liver (i.e., hepatosteatosis). NAFLD can progress to nonalcoholic steatohepatitis (NASH) in about one-third of the patients with NAFLD, thereby increasing the risk of cirrhosis and hepatocellular carcinoma (152, 153). An emerging feature of NAFLD is the decline in hepatic omega-3 and omega-6 PUFA with disease progression (154). Considering that C_{20-22} omega-3 PUFA can reduce fatty acid synthesis and inflammation, a possible therapeutic strategy would be to increase dietary intake of long-chain omega-3 PUFA. A 2018 meta-analysis of 18 randomized controlled trials in 1,424 participants with NAFLD found that omega-3 supplementation showed beneficial effects on liver fat, specific liver enzymatic activities, serum triglycerides, fasting glucose, and insulin resistance (155). However, there was no evidence of an effect on total cholesterol, LDL-cholesterol, HDL-cholesterol, fasting insulin, blood pressure, BMI, and waist circumference (155). Other recent meta-analyses have also reported that supplementation with long-chain omega-3 fatty acids from fish/seal oil (0.25-6.8 g/day for 3-25 months) improved hepatosteatosis and other metabolic disorders in both children and adults with NAFLD (reviewed in 153). Additional studies are needed to examine their efficacy in more severe cases of NASH.

Inflammatory diseases

Rheumatoid arthritis

A 2017 meta-analysis of 20 randomized controlled trials in 1,252 participants with rheumatoid arthritis assessed the efficacy of long-chain omega-3 PUFA supplementation on a series of clinical outcomes (156). Omega-3 supplementation (0.3-9.6 g/day) for 3 to 18 months reduced the number of tender joints (14 trials), as well as early morning stiffness (15 trials) and pain level (16 trials) compared to placebo. Blood concentrations of triglycerides (3 trials) and pro-inflammatory leukotriene B4 (5 trials) were also decreased with supplemental omega-3 PUFA (156). Another 2017 meta-analysis of 42 randomized controlled trials examined the effect of omega-3 supplementation (mainly as fish oil) on arthritic pain in participants diagnosed with different types of arthritis (157). Daily administration of marine-derived EPA (0.01-4.1 g) and DHA (0.01-2.7 g) for up to 18 months resulted in a reduction in patients' reported pain (using a visual analog scale [VAS] for pain) in those suffering from rheumatoid arthritis (22 trials) and those with other types of arthritis (i.e., juvenile arthritis, psoriatic arthritis) or mixed diagnoses (3 trials), yet not in those with osteoarthritis (5 trials). The evidence of an effect of omega-3 supplements in patients with rheumatoid arthritis was deemed of moderate quality (157). In a 2017 systematic review of 18 trials, including 1,143 subjects with rheumatoid arthritis, only 4 of 18 placebo-controlled trials showed a benefit of omega-3 PUFA supplementation (2.2-3.6 g/day for 12-36 weeks) on pain level — reported by patients and/or assessed by physicians (158). In most trials, the use of medications (nonsteroidal anti-inflammatory drugs [NSAIDs] and/or disease-modifying anti-rheumatic drugs [DMARDs]) was continued throughout the intervention period. Results of a few trials suggested that omega-3 PUFA could spare the need for anti-inflammatory medications in some patients yet failed to show superiority of PUFA in pain management (159, 160).

The limited body of evidence that suggests potential benefits of omega-3 supplementation in rheumatoid arthritis treatment needs strengthening with data from larger studies conducted for longer intervention periods (157, 158).

Inflammatory bowel disease

Crohn's disease: A 2013 systematic review evaluated the efficacy of omega-3 supplementation in patients with Crohn's disease, considering the evidence base from both short-term (9 to 24 weeks) and long-term (1 year) trials (161). Among five trials that evaluated the efficacy of omega-3 supplementation on relapse rates, conflicting outcomes were reported. Most trials were limited by small sample sizes and short duration — up to three years may be necessary to see an effect on relapse rates given the natural relapsing-remitting course of the disease. The two largest and most recent trials (EPIC-1 and EPIC-2) showed no significant effect of omega-3 supplementation on indicators of Crohn's disease remission compared to placebo (162). Other systematic reviews of the literature reached similar conclusions (163-165). Three short-term trials showed positive effects of omega-3 supplementation on plasma biochemical parameters (e.g., reduced inflammatory cytokine expression, increased plasma EPA and DHA concentrations) compared to controls (161). In spite of its impact on biochemical changes in the short-term, however, the ability of omega-3 supplementation to maintain remission or effect clinically meaningful changes in Crohn's disease is not supported by the current evidence (164).

Ulcerative colitis: Seven randomized controlled trials of fish oil supplementation in patients with active ulcerative colitis reported significant improvement in at least one outcome measure, such as decreased corticosteroid use, improved disease activity scores, or improved histology scores (163). In patients with inactive ulcerative colitis, omega-3 supplementation had no effect on relapse rates compared to placebo in four separate trials (163, 165).

While no serious side effects were reported in any trials of fish oil supplementation for the maintenance or remission of inflammatory bowel disease, diarrhea and upper gastrointestinal symptoms occurred more frequently with omega-3 treatment (163-165).

Asthma

Inflammatory eicosanoids (leukotrienes) derived from arachidonic acid (AA; 20:4n-6) are thought to play an important role in the pathology of asthma (32). Because increasing omega-3 fatty acid intake has been found to decrease the formation of AA-derived leukotrienes, a number of clinical trials have examined the effects of long-chain omega-3 fatty acid supplementation on asthma. Although there is some evidence that omega-3 fatty acid supplementation can decrease the production of inflammatory mediators in asthmatic patients (166, 167), evidence that omega-3 fatty acid supplementation decreases the clinical severity of asthma in controlled trials has been inconsistent (168). Three systematic reviews of randomized controlled trials of long-chain omega-3 fatty acid supplementation in asthmatic adults and children found no consistent effects on clinical outcome measures, including pulmonary function tests, asthmatic symptoms, medication use, or bronchial hyperreactivity (169-171).

Immunoglobulin A nephropathy

Immunoglobulin A (IgA) nephropathy is a kidney disorder that results from the deposition of IgA in the glomeruli of the kidneys. The cause of IgA nephropathy is not clear, but progressive renal failure may eventually develop in 15%-40% of patients (172). Since glomerular IgA deposition results in increased production of inflammatory mediators, omega-3 fatty acid supplementation could potentially modulate the inflammatory response and preserve renal function.

A 2012 meta-analysis assessed the efficacy of omega-3 fatty acid supplementation on adult IgA nephropathy (173). Five randomized controlled trials were included in an analysis involving 239 patients (mean age, 37-41 years) who received placebo or supplemental EPA + DHA at doses of 1.4 to 5.1 g/day for 6 to 24 months. Compared with control groups, omega-3 supplementation had no significant effect on urine protein excretion or glomerular filtration rate. Only two trials measured changes in serum creatinine (a marker of renal function) and end-stage renal disease — omega-3 treatment had a beneficial effect on these two parameters in both trials. No adverse events associated with omega-3 supplementation were reported in any of the trials. A more recent review of the literature identified six trials showing evidence of omega-3 supplementation slowing IgA nephropathy disease progression and three trials reporting no effect (174). Additionally, preliminary data suggested that the potential synergistic actions of aspirin and long-chain omega-3 PUFAs might constitute a promising treatment option (168).

Neuropsychiatric disorders

Autism spectrum disorders

Autism spectrum disorders (ASD) refer to three neurodevelopmental disorders of variable severity, namely autism, Asperger syndrome, and pervasive development disorder. ASD are characterized by abnormal information processing in the brain due to alterations in the way nerve cells and their synapses connect and organize. ASD are thought to have a strong genetic basis, yet environmental factors including diet may play an important role. Given that omega-3 and omega-6 PUFA are necessary for neuronal growth and synapse formation (see Biological Activities), they may be of significant benefit in the prevention and/or management of ASD. This is supported by observations of PUFA abnormalities in blood of children with ASD, when compared to their peers with no neurodevelopmental disorders (175). A meta-analysis of case-control studies reported lower blood concentrations of DHA and EPA in children with ASD compared to typically developing children; yet, the ratio of total omega-6 to omega-3 fatty acids was similar between children with and without ASD symptoms (176). A systematic review by the same authors identified six randomized controlled trials that examined the effect of primarily long-chain omega-3 PUFA on ASD symptoms (176). All the studies included children; one study also included adults ≤28 years (177). Four trials used EPA (0.70-0.84 g/day) plus DHA (0.46-0.70 g/day) (178-181), one trial used DHA (0.24 g/day) plus AA (0.24 g/day) (177), and one trial only used only DHA (0.20 g/day) (182). A pooled analysis of four (177-180) of these trials, including a total of 107 participants, showed a small improvement in measures of social interaction and repetitive and restrictive interests and behaviors with long-chain PUFA supplementation for 6 to 16 weeks; however, there was no effect on measures of communication and ASD co-existing conditions, such as hyperactivity, irritability, sensory issues, and gastrointestinal symptoms (176). Two additional systematic reviews and meta-analyses, also published in 2017, identified the same set of trials. One meta-analysis suggested a benefit of long-chain PUFA on measures of lethargy and stereotypy but found no overall clinical improvement compared to placebo (183). The other meta-analysis suggested an improvement regarding lethargy yet a worsening of externalizing behavior and social skills in children supplemented with omega-3 PUFA (184).

The available evidence is based on few trials of small sample sizes and is thus too limited to draw firm conclusions regarding the potential benefit of long-chain PUFA supplementation in ASD management.

Major depression and bipolar disorder

Data from ecologic studies across different countries suggested an inverse association between seafood consumption and national rates of major depression (185) and bipolar disorder (186).

Several small studies have found omega-3 fatty acid concentrations to be lower in plasma (187-189) and adipose tissue (190) of individuals suffering from depression compared to controls. Although it is not known how omega-3 fatty acid intake affects the incidence of depression, modulation of neuronal signaling pathways and eicosanoid production have been proposed as possible mechanisms (191). There may be some benefit of omega-3 PUFA supplementation on depressive disorders, but it is difficult to compare studies and draw conclusions due to great heterogeneity among the trials (192, 193). Small sample sizes, lack of standardization of therapeutic doses, type of omega-3 PUFA administered, co-treatment with pharmacological agents, and diagnostic criteria vary among the trials. A 2012 systematic review of all published randomized controlled trials investigated the effect of omega-3 PUFA supplementation on the prevention and treatment of several types of depression and other neuropsychiatric disorders (192). With respect to major depression, most studies reported a positive effect of omega-3 supplements on depressive symptoms, though efficacy is still considered inconclusive given the great variability among trials. A few themes emerged from this review: more trials reported positive effect for omega-3 PUFA supplements as an adjunct to pharmacological treatment; in monotherapy trials, EPA alone was more effective than DHA alone; and in combination trials, positive effects were more likely if an EPA:DHA ratio of >1.5–2.0 was administered.

A 2014 meta-analysis grouped trials by type of diagnosis of depression (194). A positive effect of omega-3 supplementation was found in 11 trials in participants with a diagnosis of major depressive disorder (according to the Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria). Omega-3 supplementation also appeared to be effective in the pooled analysis of eight trials in participants not formally diagnosed with major depressive disorder, i.e., adults with depressive symptoms despite ongoing treatment, untreated patients with mild-to-severe depressed mood, patients with a history of at least one major depressive episode, women with borderline personality disorder, patients with recurrent self-harm, and postmenopausal women with psychological distress and depressive symptoms. There was no mood improvement with omega-3 supplements in generally healthy adults experiencing depressive symptoms, as suggested by the pooled analysis of six trials (194).

Finally, a 2017 Cochrane systematic review and meta-analysis of 20 randomized controlled trials reported a small benefit of omega-3 supplementation on depressive symptoms when compared to placebo, yet the evidence was deemed of very low quality and the positive effect was judged likely to be biased and not clinically significant (195).

Unipolar depression and bipolar disorder are considered distinct psychiatric conditions, although major depression occurs in both. A 2016 meta-analysis of eight case-control studies that compared the PUFA composition of red blood cell membranes between patients with bipolar disorder and healthy subjects showed abnormally low red blood cell DHA concentrations with bipolar disorder (196). As with major depression, reviews of trials indicated that omega-3 supplementation may have a positive effect as an adjunct to therapy in patients with bipolar disorder (192, 194). Additionally, a 2016 randomized, placebo-controlled trial in 100 participants with bipolar disorder reported a reduction in the severity of manic episodes with daily supplementation of 1,000 mg omega-3 PUFA for three months (197).

While there is some promising evidence for the use of omega-3 fatty acids for major depression and bipolar disorder, additional trials that account for dietary omega-3 intake, changes in red blood cell PUFA concentrations, the ratio of EPA:DHA provided, and co-treatment with medications are necessary.

Schizophrenia

A 2013 meta-analysis of 18 studies compared the PUFA composition of red blood cell membranes in patients with schizophrenia to individuals without the disorder (198). The majority of studies investigated medicated patients, though the authors separated the analysis into three groups of patients at time of measurement in order to account for possible confounding from pharmacologic agents: antipsychotic-medicated, antipsychotic-naïve, and antipsychotic-free. Overall, decreased concentrations of DPA, DHA, and AA in red blood cell membranes were associated with the schizophrenic state. Several mechanisms may account for PUFA abnormalities in schizophrenia, such as altered lipid metabolism, increased oxidative stress, or changes in diet consequent to disease-related behavior.

The use of long-chain omega-3 fatty acid supplements to alleviate symptoms of schizophrenia or to mitigate adverse effects of antipsychotic medications has been investigated in a number of clinical trials (194, 199). In a recent randomized, placebo-controlled trial in 50 subjects with recent onset of schizophrenia who were medicated, daily supplementation with EPA (740 mg) and DHA (400 mg) reduced psychotic symptoms (assessed with the Brief Psychiatric Rating Scale) only in those who were not taking the anxiolytic, lorazepam (Ativan) (200). Overall, however, there was no effect of long-chain PUFA supplements on schizophrenia symptoms. Yet, given the high safety profile of fish oil supplements and some evidence of a positive effect of EPA supplementation in a subset of trials, some clinicians may consider EPA a useful adjunct to antipsychotic therapy in patients with schizophrenia.

Alzheimer's disease and dementia

Several mechanisms suggest that omega-3 PUFA supplementation may improve the cognitive performance of individuals with Alzheimer's disease and other types of dementia. In particular, the antioxidative and anti-inflammatory properties of these PUFA may help protect neurons, promote synaptic plasticity, and limit cellular death. The PUFA composition of the diet appears to influence blood cholesterol, which may play a role in the pathology of Alzheimer's disease. However, the current evidence from clinical trials is not supportive of omega-3 supplementation in the treatment of Alzheimer's disease in humans. A 2016 Cochrane review identified three randomized, placebo-controlled trials in patients with Alzheimer's disease of mild-to-moderate severity (201). These trials compared daily supplementation with DHA (between 675 mg and 1,700 mg) and EPA (between 600 mg and 975 mg) to a placebo for 12 months (202, 203) or 18 months (204). Of note, the study by Quinn et al. (204) also included 4 mg/day of vitamin E (used as preservative — see also Nutrient interactions) in the intervention arm, and the study by Freund-Levi et al. (202) included DHA (900-1,100 mg/day) but no EPA. The pooled analysis of these trials showed no beneficial effect of omega-3 supplementation on measures of global and specific cognitive functions, measures of functional outcomes, and measures of dementia severity (201). There was no difference between intervention and placebo arms regarding the occurrence of adverse effects (201).

Sources

Food sources

Humans can synthesize arachidonic acid (AA) from linoleic acid (LA) and eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) from α-linolenic acid (ALA) through a series of desaturation and elongation reactions. EPA and docosapentaenoic acid (DPA) are also obtained from the retroconversion of DHA (see Metabolism and Bioavailability). Due to low conversion efficiency, it is advised to obtain EPA and DHA from additional sources.

Omega-6 fatty acids

Linoleic acid (LA): Food sources of LA include vegetable oils, such as soybean, safflower, and corn oil; nuts; seeds; and some vegetables. Dietary surveys in the US indicate that the average adult intake of LA ranges from 17 to 20 g/day for men and 12 to 13 g/day for women (78). Some foods that are rich in LA are listed in **Table 2**.

Table 2. Food Sources of Linoleic Acid (18:2n-6) (205)

Food	Serving	Linoleic Acid (g)
Safflower oil	1 tablespoon	10.1
Sunflower seeds, oil roasted	1 ounce	9.7
Pine nuts	1 ounce	9.4
Sunflower oil	1 tablespoon	8.9
Corn oil	1 tablespoon	7.3
Soybean oil	1 tablespoon	6.9
Pecans, oil roasted	1 ounce	6.4
Brazil nuts	1 ounce	5.8
Sesame oil	1 tablespoon	5.6

Arachidonic acid: Animals, but not plants, can convert LA to AA. Therefore, AA is absent in vegetable oils and fats and present in small amounts in meat, poultry, and eggs.

Omega-3 fatty acids

α-Linolenic acid (ALA): Flaxseeds, walnuts, and their oils are among the richest dietary sources of ALA. Canola oil is also an excellent source of ALA. Dietary surveys in the US indicate that average adult intakes for ALA range from 1.8 to 2.0 g/day for men and from 1.4 to 1.5 g/day for women (78). Some foods that are rich in ALA are listed in **Table 3**.

Table 3. Food Sources of α-Linolenic Acid (18:3n-3) (205)

Food	Serving	α-Linolenic acid (g)
Flaxseed oil	1 tablespoon	7.3
Chia seeds, dried	1 ounce	5.1
Walnuts, English	1 ounce	2.6
Flaxseeds, ground	1 tablespoon	1.6
Walnut oil	1 tablespoon	1.4
Canola oil	1 tablespoon	1.3
Soybean oil	1 tablespoon	0.9
Mustard oil	1 tablespoon	0.8
Walnuts, black	1 ounce	0.6
Tofu, firm	½ cup	0.2

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): Dietary surveys in the US indicate that average adult intakes of EPA range from 0.03 to 0.06 g/day, and average adult intakes of DHA range from 0.05 to 0.10 g/day (78). Oily fish are the major dietary source of EPA and DHA; omega-3 fatty acid-enriched eggs are also available in the US. Some foods that are rich in EPA and DHA are listed in **Table 4**.

Table 4. Food Sources of EPA (20:5n-3) and DHA (22:6n-3) (107)

Food	Serving	EPA (g)	DHA (g)	Amount Providing 1 g of EPA + DHA
Herring, Pacific	3 ounces*	1.06	0.75	1.5 ounces
Salmon, chinook	3 ounces	0.86	0.62	2 ounces
Sardines, Pacific	3 ounces	0.45	0.74	2.5 ounces
Salmon, Atlantic	3 ounces	0.28	0.95	2.5 ounces
Oysters, Pacific	3 ounces	0.75	0.43	2.5 ounces
Salmon, sockeye	3 ounces	0.45	0.60	3 ounces
Trout, rainbow	3 ounces	0.40	0.44	3.5 ounces
Tuna, canned, white	3 ounces	0.20	0.54	4 ounces
Crab, Dungeness	3 ounces	0.24	0.10	9 ounces
Tuna, canned, light	3 ounces	0.04	0.19	12 ounces
*A three-ounce serving of fish is about the size of a deck of cards.				

Supplements

Omega-6 fatty acids

Borage seed oil, evening primrose oil, and black currant seed oil are rich in γ-linolenic acid (GLA; 18:3n-6) and are often marketed as GLA or essential fatty acid (EFA) supplements (206).

Omega-3 fatty acids

Flaxseed oil (also known as flax oil or linseed oil) is available as an ALA supplement. A number of fish oils are marketed as omega-3 fatty acid supplements. The omega-3 fatty acids from natural fish oil are in the triglyceride form, often with only one of three attached fatty acids an omega-3; thus, up to 70% of fatty acids provided may be other types (3). Ethyl esters of EPA and DHA (ethyl-EPA and ethyl-DHA) are concentrated sources of long-chain omega-3 fatty acids that provide more EPA and DHA per gram of oil. Krill oil contains both EPA and DHA and is considered comparable to fish oil as a source of these long-chain PUFA (207). Cod liver oil is also a rich source of EPA and DHA, but some cod liver oil preparations may contain excessive amounts of preformed vitamin A (retinol) and vitamin D (206). DHA supplements derived from algal and fungal sources are also available. Because dietary DHA can be retroconverted to EPA and DPA in humans, DHA supplementation represents yet another alternative to fish oil supplements (see Metabolism and Bioavailability).

The content of EPA and DHA varies in each of these preparations, making it necessary to read product labels in order to determine the EPA and DHA levels provided by a particular supplement. All omega-3 fatty acid supplements are absorbed more efficiently with meals. Dividing one's daily dose into two or three smaller doses throughout the day will decrease the risk of gastrointestinal side effects (see Safety).

Infant formula

In 2001, the FDA began permitting the addition of DHA and AA to infant formula in the United States (208). Presently, manufacturers are not required to list the amounts of DHA and AA added to infant formula on the label. However, most infant formula manufacturers provide this information. The amounts added to formulas in the US range from 8 to 17 mg DHA/100 calories (5 fl oz) and from 16 to 34 mg AA/100 calories. For example, an infant drinking 20 fl oz of DHA-enriched formula daily would receive 32 to 68 mg/day of DHA and 64 to 136 mg/day of AA.

Safety

Adverse effects

γ-Linolenic acid (18:3n-6)

Supplemental γ-linolenic acid is generally well tolerated, and serious adverse side effects have not been observed at doses up to 2.8 g/day for 12 months (209). High doses of borage seed oil, evening primrose oil, or black currant seed oil may cause gastrointestinal upset, loose stools, or diarrhea (206). Because of case reports that supplementation with evening primrose oil induced seizure activity in people with undiagnosed temporal lobe epilepsy (210), people with a history of seizures or a seizure disorder are generally advised to avoid evening primrose oil and other γ-linolenic acid-rich oils (206).

α-Linolenic acid (18:3n-3)

Although flaxseed oil is generally well tolerated, high doses may cause loose stools or diarrhea (211). Allergic and anaphylactic reactions have been reported with flaxseed and flaxseed oil ingestion (212).

Eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)

Serious adverse reactions have not been reported in those using fish oil or other EPA and DHA supplements. The most common adverse effect of fish oil or EPA and DHA supplements is a fishy aftertaste. Belching and heartburn have also been reported. Additionally, high doses may cause nausea and loose stools.

Potential for excessive bleeding: The potential for high omega-3 fatty acid intakes, especially EPA and DHA, to prolong bleeding times has been well studied and may play a role in the cardioprotective effects of omega-3 fatty acids. Although excessively long bleeding times and increased incidence of hemorrhagic stroke have been observed in Greenland Eskimos with very high intakes of EPA + DHA (6.5 g/day), it is not known whether high intakes of EPA and DHA are the only factor responsible for these observations (1). The US FDA has ruled that intakes up to 3 g/day of long-chain omega-3 fatty acids (EPA and DHA) are Generally Recognized As Safe (GRAS) for inclusion in the diet, and available evidence suggests that intakes less than 3 g/day are unlikely to result in clinically significant bleeding (107). Although the US Institute of Medicine did not establish a tolerable upper intake level (UL) for omega-3 fatty acids, caution was advised with the use of supplemental EPA and DHA, especially in those who are at increased risk of excessive bleeding (see Drug interactions and Nutrient interactions) (1, 206).

Potential for immune system suppression: Although the suppression of inflammatory responses resulting from increased omega-3 fatty acid intakes may benefit individuals with inflammatory or autoimmune diseases, anti-inflammatory doses of omega-3 fatty acids could decrease the potential of the immune system to destroy pathogens (213). Studies comparing measures of immune cell function outside the body (*ex vivo*) at baseline and after supplementing people with omega-3 fatty acids, mainly EPA and DHA, have demonstrated immunosuppressive effects at doses as low as 0.9 g/day for EPA and 0.6 g/day for DHA (1). Although it is not clear if these findings translate to impaired immune responses *in vivo*, caution should be observed when considering omega-3 fatty acid supplementation in individuals with compromised immune systems.

Potential other effects: Although fish oil supplements are unlikely to affect glucose homeostasis, people with diabetes mellitus who are considering fish oil supplements should inform their physician and be monitored if they choose to take them (206).

Infant formula

In early studies of DHA-enriched infant formula, EPA- and DHA-rich fish oil was used as a source of DHA. However, some preterm infants receiving fish oil-enriched formula had decreased plasma AA concentrations, which were associated with decreased weight (but not length and head circumference) (214, 215). This effect was attributed to the potential for high concentrations of EPA to interfere with the synthesis of AA, which is essential for normal growth. Consequently, EPA was removed and AA was added to DHA-enriched formula. Currently available infant formulas in the US contain only AA and DHA derived from algal or fungal sources, rather than fish oil. Randomized controlled trials have not found any adverse effects on growth in infants fed formulas enriched with AA and DHA for up to one year (216).

Pregnancy and lactation

The safety of supplemental omega-3 and omega-6 fatty acids, including borage seed oil, evening primrose oil, black currant seed oil, and flaxseed oil, has not been established in pregnant or lactating (breast-feeding) women (217). Studies of fish oil supplementation during pregnancy and lactation have not reported any serious adverse effects, but use of omega-6/omega-3 PUFA-containing supplements and fish oil supplements in pregnant or nursing women should be monitored by a physician (see Contaminants in fish and Contaminants in supplements) (206).

Contaminants in fish

Some species of fish may contain significant levels of methylmercury, polychlorinated biphenyls (PCBs), or other environmental contaminants (218). In general, larger predatory fish, such as swordfish, tend to contain the highest levels of these contaminants. Removing the skin, fat, and internal organs of the fish prior to cooking and allowing the fat to drain from the fish while it cooks will decrease exposure to a number of fat-soluble pollutants, such as PCBs (219). However, methylmercury is found throughout the muscle of fish, so these cooking precautions will not reduce exposure to methylmercury. Organic mercury compounds are toxic and excessive exposure can cause brain and kidney damage. The developing fetus, infants, and young children are especially vulnerable to the toxic effects of mercury on the brain. In order to limit their exposure to methylmercury, the US Food and Drug Administration (FDA) and Environmental Protection Agency have formulated joint recommendations for women who may become pregnant, pregnant women, breast-feeding women, and parents. These recommendations are presented in **Table 5**.

For more information about the FDA/Environmental Protection Agency advisory for pregnant women and parents of young children on eating fish, see their online brochure. More information about mercury levels in commercial fish and shellfish is available from the FDA.

Of note, the 2015-2020 Dietary Guidelines for Americans recommend the consumption of salmon, anchovies, herring, shad, sardines, Pacific oysters, trout, and Atlantic and Pacific mackerel (not king mackerel), which are higher in EPA and DHA and lower in methylmercury (220).

Contaminants in supplements

Although concerns have been raised regarding the potential for omega-3 fatty acid supplements derived from fish oil to contain methylmercury, PCBs, and dioxins, several independent laboratory analyses in the US have found commercially available omega-3 fatty acid supplements to be free of methylmercury, PCBs, and dioxins (221). The absence of methylmercury in omega-3 fatty acid supplements can be explained by the fact that mercury accumulates in the muscle, rather than the fat of fish (107). In general, fish body oils contain lower concentrations of PCBs and other fat-soluble contaminants than fish liver oils. Additionally, fish oils that have been more highly refined and deodorized contain lower concentrations of PCBs (222). Pyrrolizidine alkaloids, potentially hepatotoxic and carcinogenic compounds, are found in various parts of the borage plant. People who take borage oil supplements should use products that are certified free of unsaturated pyrrolizidine alkaloids (206).

Table 5. Recommendations to Limit Exposure to Seafood Methylmercury (219)

1. Eat 8-12 ounces of a variety of fish a week	• That’s 2 or 3 servings of fish a week • For young children, give them 2 or 3 servings of fish a week with the portion right for the child’s age and calorie needs.
2. Choose fish lower in mercury.	• Many of the most commonly eaten fish are lower in mercury. • Examples include salmon, shrimp, pollock, tuna (light canned), tilapia, catfish, and cod.
3. Avoid 4 types of fish: tilefish from the Gulf of Mexico, shark, swordfish, and king mackerel.	• These 4 types of fish are highest in mercury. • Limit white (albacore) tuna to 6 ounces a week.
4. When eating fish you or others have caught from streams, rivers, and lakes, pay attention to fish advisories on those waterbodies.	• If advice isn’t available, adults should limit such fish to 6 ounces a week and young children to 1 to 3 ounces a week and not eat other fish that week.
5. When adding more fish to your diet, be sure to stay within your calorie needs.	

Drug interactions

γ-Linolenic acid supplements, such as evening primrose oil or borage seed oil, may increase the risk of seizures in people on phenothiazines (neuroleptic agents), such as chlorpromazine (210). High doses of black currant seed oil, borage seed oil, evening primrose oil, flaxseed oil, and fish oil may inhibit platelet aggregation; therefore, these supplements should be used with caution in people on anticoagulant medications (206). In particular, people taking fish oil or long-chain omega-3 fatty acid (EPA and DHA) supplements in combination with anticoagulant drugs, including aspirin, clopidogrel (Plavix), dalteparin (Fragmin), dipyridamole (Persantine), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), and warfarin (Coumadin), should have their coagulation status monitored using a standardized prothrombin time assay (international normalized ratio [INR]). One small study found that 3 g/day or 6 g/day of fish oil did not affect INR values in 10 patients on warfarin over a four-week period (223). However, a case report described an individual who required a reduction of her warfarin dose when she doubled her fish oil dose from 1 g/day to 2 g/day (224).

Nutrient interactions

Vitamin E

Outside the body, PUFA become rancid (oxidized) more easily than saturated fatty acids. Fat-soluble antioxidants, such as vitamin E (α-tocopherol), play an important role in preventing the oxidation of PUFA. Inside the body, results of animal studies and limited data in humans suggest that the amount of vitamin E required to prevent lipid peroxidation increases with the amount of PUFA consumed (225). One widely used recommendation for vitamin E intake is 0.6 mg of α-tocopherol per gram of dietary PUFA. This recommendation was based on a small study in men and the ratio of α-tocopherol to LA in the US diet and has not been verified in more comprehensive studies. Although EPA and DHA are easily oxidized outside the body, it is presently unclear whether they are more susceptible to oxidative damage within the body (226). High vitamin E intakes have not been found to decrease biomarkers of oxidative damage when EPA and DHA intakes are increased (227, 228), but some experts believe that an increase in PUFA intake, particularly omega-3 PUFA intake, should be accompanied by an increase in vitamin E intake (1).

Intake Recommendations

US Institute of Medicine

The Food and Nutrition Board of the US Institute of Medicine (now the National Academy of Medicine) has established adequate intake (AI) for omega-6 and omega-3 fatty acids (**Tables 6 and 7**) (1).

Table 6. Adequate Intake (AI) for Omega-6 Fatty Acids (1)

Life Stage	Age	Source	Males (g/day)	Females (g/day)
Infants	0-6 months	Omega-6 PUFA*	4.4	4.4
Infants	7-12 months	Omega-6 PUFA*	4.6	4.6
Children	1-3 years	LA#	7	7
Children	4-8 years	LA	10	10
Children	9-13 years	LA	12	10
Adolescents	14-18 years	LA	16	11
Adults	19-50 years	LA	17	12
Adults	51 years and older	LA	14	11
Pregnancy	all ages	LA	-	13
Breast-feeding	all ages	LA	-	13
*The various omega-6 polyunsaturated fatty acids (PUFA) present in human milk can contribute to the AI for infants. # LA, linoleic acid				

Table 7. Adequate Intake (AI) for Omega-3 Fatty Acids (1)

Life Stage	Age	Source	Males (g/day)	Females (g/day)
Infants	0-6 months	ALA, EPA, DHA*	0.5	0.5
Infants	7-12 months	ALA, EPA, DHA	0.5	0.5
Children	1-3 years	ALA	0.7	0.7
Children	4-8 years	ALA	0.9	0.9
Children	9-13 years	ALA	1.2	1.0
Adolescents	14-18 years	ALA	1.6	1.1
Adults	19 years and older	ALA	1.6	1.1
Pregnancy	all ages	ALA	-	1.4
Breast-feeding	all ages	ALA	-	1.3
*All omega-3 polyunsaturated fatty acids present in human milk can contribute to the AI for infants. ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.				

Given the established health benefits of consuming at least two servings of oily fish per week, providing approximately 400 to 500 mg EPA + DHA, some researchers have proposed that the US Institute of Medicine (now the National Academy of Medicine) establish dietary reference intakes (DRIs) for EPA + DHA (27). For now, there are no DRIs for EPA and DHA specifically.

Because maternal dietary intake of long-chain PUFA determines the DHA status of the newborn, several expert panels in the US recommend that pregnant and lactating women consume at least 200 mg DHA per day, close to the amount recommended for adults in general (250 mg/day) (70, 229). The potential benefits associated with obtaining long-chain omega-3 fatty acids through moderate consumption of fish (e.g., 1-2 servings weekly) during pregnancy and lactation outweigh any risks of contaminant exposure, though fish with high concentrations of methylmercury should be avoided (218). For information about contaminants in fish and guidelines for fish consumption by women of childbearing age, see Contaminants in fish.

2015-2020 Dietary Guidelines for Americans

The 2015-2020 Dietary Guidelines provide recommendations for nutritional goals for linoleic acid and α-linolenic acid based on the DRIs (see **Tables 6 and 7**). Seafood, nuts, seeds, and oils, which are all part of healthy dietary patterns, provide essential fatty acids. The 2015-2020 Dietary Guidelines provide dietary recommendations regarding the amounts of these foods for those who choose to follow a healthy US-style eating pattern, a healthy Mediterranean-style eating pattern, or a healthy vegetarian eating pattern (**Table 8**).

Table 8. 2015-2020 Dietary Guidelines for Americans’ Recommendations for Sources of Omega-3 and Omega-6 Polyunsaturated Fatty Acids* (220)

	Healthy Eating Patterns		
Food	US-style	Mediterranean-style	Vegetarian
Seafood (oz-eq/week)	8	15	–
Nuts, seeds, soy products (oz-eq/week)	5	5	7
Oils (g/week)	27	27	27
*Recommendations for total daily energy needs of 2,000 calories per day. Estimates of daily calorie needs according to age, gender, and physical activity can be found in the Appendix 2 of the ‘2015-2020 Dietary Guidelines for Americans’ report (220). Oz-eq, ounce-equivalent			

American Heart Association recommendation

The American Heart Association recommends that people without documented coronary heart disease (CHD) eat a variety of fish (preferably oily) at least twice weekly (230). Two servings of oily fish provide approximately 500 mg of EPA plus DHA. Pregnant women and children should avoid fish that typically have higher levels of methylmercury (see Contaminants in fish). People with documented CHD and those with heart failure without preserved left ventricular function are advised to consume approximately 1 g/day of EPA + DHA preferably from oily fish, or to consider EPA + DHA supplements in consultation with a physician (104, 107). Patients who need to lower serum triglycerides may take 2 to 4 g/day of EPA + DHA supplements under a physician's care (see Hypertriglyceridemia).

International recommendations

Upon request of the European Commission, the European Food Safety Authority (EFSA) proposed adequate intakes (AI) for the essential fatty acids LA and ALA, as well as the long-chain omega-3 fatty acids EPA and DHA (231). EFSA recommends an LA intake of 4% of total energy and an ALA intake of 0.5% of total energy; an AI of 250 mg/day is recommended for EPA plus DHA (232). The European Food and Safety Authority (EFSA) recommends that pregnant and lactating women consume an additional 100 to 200 mg of preformed DHA on top of the 250 mg/day EPA plus DHA recommended for healthy adults (231).

For adults, the World Health Organization recommends an acceptable macronutrient distribution range (AMDR) for omega-6 fatty acid intake of 2.5%-9% of energy and for omega-3 fatty acid intake of 0.5%-2% of energy (233). Their AMDR for EPA plus DHA is 0.25 to 2 g/day (the upper level applying to secondary prevention of coronary heart disease).

The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommends healthy adults have an LA intake of 2% energy, an ALA intake of 0.7% energy, and a minimum of 500 mg/day of EPA plus DHA for cardiovascular health (234).

Linus Pauling Institute recommendation

The Linus Pauling Institute supports the AI for the essential fatty acids (see Tables 6 and 7) and recommends that generally healthy adults increase their intake of long-chain omega-3 fatty acids by eating fish twice weekly and consuming foods rich in ALA, such as walnuts, flaxseeds, and flaxseed or canola oil. If you don't regularly consume fish, consider taking a two-gram fish oil supplement several times a week. If you are prone to bleeding or take anticoagulant drugs, consult your physician.

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Fiber

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Summary

- Dietary fiber is a diverse group of compounds, including lignin and complex carbohydrates, which cannot be digested by human enzymes in the small intestine. *(More information)*
- Although each fiber type is chemically unique, fibers can be classified according to their solubility, viscosity, and fermentability in order to better understand their physiological effects. *(More information)*
- Soluble gel-forming fibers, such as psyllium and fibers found in oat products, can lower serum LDL cholesterol concentrations and normalize blood glucose and insulin responses. *(More information)*

- Improving glycemic control
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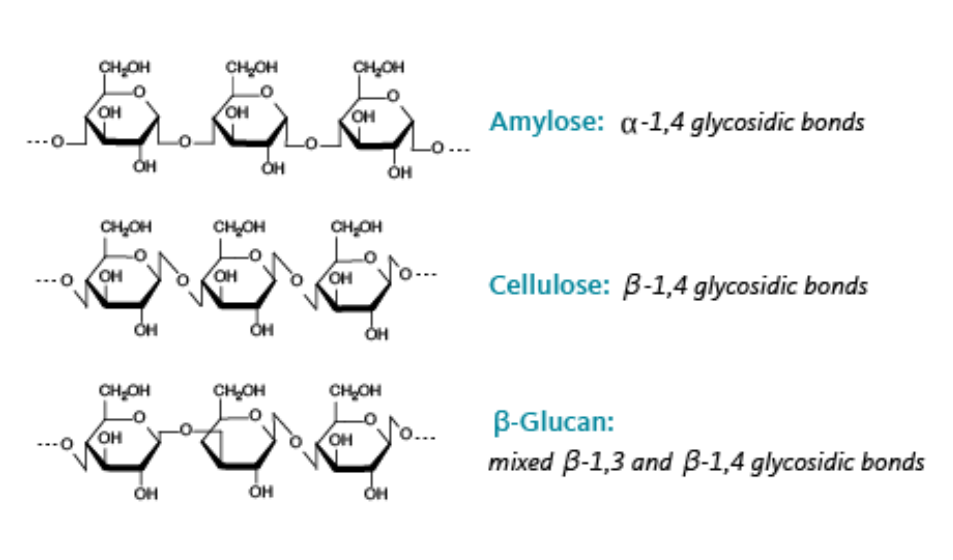
- Large/coarse insoluble fibers (e.g., wheat bran) and nonfermentable, soluble gel-forming fibers (e.g., psyllium) can have a potential laxative effect. *(More information)*
- Large prospective cohort studies consistently report inverse associations between consumption of diets rich in fiber and risks of cardiovascular disease and type 2 diabetes mellitus. *(More information)*
- A review of the most recent meta-analyses of observational studies suggests that dietary fiber consumption is inversely associated with the risk of cancer of the esophagus, stomach, colon, pancreas, ovary, and breast. *(More information)*
- Both consumption of fiber-rich diets and supplementation with soluble gel-forming fibers could help improve glycemic control in individuals with type 1 or type 2 diabetes mellitus. *(More information)*
- The Adequate Intake (AI) recommendation for total daily fiber intake is 38 g/day for men and 25 g/day for women. However, the average American consumes only about 17 g/day of dietary fiber, and dietary fiber intake might be closer to 10 g/day in those following a low-carbohydrate diet. *(More information)*
- Some strategies for increasing dietary fiber intake include increasing fruit and nonstarchy vegetable intake, increasing intake of legumes, eating whole-grain cereal or oatmeal for breakfast, substituting whole grains for refined grains, and substituting nuts or popcorn for less healthy snacks. *(More information)*

Introduction

All dietary fibers are resistant to digestion in the small intestine, meaning they arrive intact in the large intestine (1). Although most fibers are carbohydrates, one important factor that determines their susceptibility to digestion by human enzymes is the conformation of the chemical bonds between sugar molecules (glycosidic bonds). Humans lack digestive enzymes capable of hydrolyzing (breaking apart) most β-glycosidic bonds, which explains why amylose, a glucose polymer with α-1,4 glycosidic bonds, is digestible by human enzymes, while cellulose, a glucose polymer with β-1,4 glycosidic bonds, is indigestible (**Figure 1**).

Figure 1. Chemical Structures of Amylose, Cellulose, and β-Glucan



CH₂OH
OH
Amylose: α-1,4 glycosidic bonds
Cellulose: β-1,4 glycosidic bonds
β-Glucan:
mixed β-1,3 and β-1,4 glycosidic bonds

[Figure 1 - Click to Enlarge]

Definitions of Fiber

Although nutritional scientists and clinicians generally agree that a healthy diet should include plenty of fiber-rich foods, agreement on the actual definition of fiber has been more difficult to achieve (2-4). In the 1970s, dietary fiber was defined as remnants of plant cells that are resistant to digestion by human enzymes (5). This definition includes a component of some plant cell walls called lignin, as well as indigestible carbohydrates found in plants. However, this definition omits indigestible carbohydrates derived from animal sources (e.g., chitin) and synthetic (e.g., fructooligosaccharides, polydextrose, wheat dextrin) and carbohydrates that are inaccessible to human digestive enzymes (e.g., resistant starch) (6). These compounds share many of the characteristics of fiber present in plant foods.

Institute of Medicine: dietary, functional, and total fiber

Before establishing intake recommendations for fiber in 2001, a panel of experts convened by the Institute of Medicine (now the National Academy of Medicine) developed definitions of fiber that made a distinction between fiber that occurs naturally in plant foods (dietary fiber) and isolated or synthetic fibers that may be added to foods or used as dietary supplements (functional fiber) (4). However, these distinctions are controversial, and there are other classification systems for dietary fiber (see Other classification systems below).

Dietary fiber

- **Lignin:** Lignin is not a carbohydrate; rather, it is a polyphenolic compound with a complex three-dimensional structure that is found in the cell walls of woody plants and seeds (7).
- **Cellulose:** Cellulose is a glucose polymer with β-1,4 glycosidic bonds found in all plant cell walls (**Figure 1**) (6).
- **β-Glucans:** β-Glucans are glucose polymers with a mixture of β-1,4 glycosidic bonds and β-1,3 glycosidic bonds (**Figure 1**). Oats and barley are particularly rich in β-glucans (7).
- **Hemicelluloses:** Hemicelluloses are a diverse group of polysaccharides (sugar polymers) containing different types of sugar monomers, including glucose, xylose, arabinose, mannose, galactose, rhamnose, or pentose. Glucomannan is a hemicellulose containing about 60% of mannose and 40% of glucose bonded together by β-1,4 glycosidic linkages. Like cellulose, hemicelluloses are found in plant cell walls.
- **Pectins:** Pectins are linear polysaccharides made of 300 to 1,000 monosaccharides, primarily galacturonic acid residues linked together by α-1,4 glycosidic bonds (8). Pectins are soluble viscous fibers that are particularly abundant in berries and other fruit (4).
- **Gums:** Gums are viscous polysaccharides often found in seeds (4). Guar gum extracted from guar beans is a galactomannan polysaccharide composed of mannose and galactose residues. It is used in the food industry for its thickening and stabilizing properties. The viscosity of guar gum is lost when guar gum is partially hydrolyzed to derive partially hydrolyzed guar gum (PHGG).
- **Inulin and oligofructose:** Inulin is a mixture of fructose chains that vary in length and often terminate with a glucose molecule (9). Oligofructose is a mixture of shorter fructose chains that may terminate in glucose or fructose. Inulin and oligofructose occur naturally in plants, such as onions and Jerusalem artichokes.
- **Resistant starch:** Naturally occurring resistant starch is sequestered in plant cell walls and is therefore inaccessible to human digestive enzymes (4). It is fermented by bacteria in the colon. Bananas and legumes are sources of naturally occurring resistant starch. Resistant starch may also be formed by food processing or by cooling and reheating.

Functional fiber

According to the Institute of Medicine's definition, functional fiber "consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans" (4). Functional fibers may be nondigestible carbohydrates that have been isolated or extracted from a natural plant or animal source, or they may be manufactured or synthesized. However, designation as a functional fiber by the Institute of Medicine requires the presentation of sufficient evidence of physiological benefit in humans. Fibers identified as potential functional fibers by the Institute of Medicine include:

- Isolated or extracted forms of the dietary fibers listed above.
- **Psyllium:** Psyllium refers to viscous, gel-forming mucilage, which is isolated from the outer coat (husk) of psyllium seeds — known in India as ispaghula husk — from the plant *Plantago ovata* or blond psyllium (4).
- **Chitin and chitosan:** Chitin is a polysaccharide polymer extracted from the exoskeletons of crustaceans, such as crab and lobster. It is a polymer of more than 5,000 acetylated glucosamine units linked by β-1,4 glycosidic bonds. Deacetylated chitin or chitosan thus consists in unbranched chains of glucosamine (8).
- **Fructooligosaccharides:** Fructooligosaccharides are short, synthetic fructose chains terminating with a glucose unit. They are used as food additives (9).
- **Galactooligosaccharides:** Galactooligosaccharides are produced through the enzymatic conversion of lactose and are classified as prebiotics (10).
- **Polydextrose and polyols:** Polydextrose and polyols are synthetic carbohydrates. Polydextrose is made of glucose and sorbitol (a sugar alcohol) and may be used as bulking agent in food. Polyols are non-sugar molecules containing multiple hydroxyl groups (-OH). Polydextrose and polyols are used as sugar substitutes in food (4).
- **Resistant dextrins:** Resistant dextrins, also called resistant maltodextrins, are synthetic indigestible polysaccharides formed when starch is heated and treated with enzymes. They are used as food additives (4).

Total fiber

Total fiber is defined by the Institute of Medicine as "the sum of dietary fiber and functional fiber" (4).

Other classification systems

Fibers can be classified into four clinically meaningful categories according to their physiochemical properties, i.e., their solubility, viscosity, and fermentability (reviewed in 11):

Soluble, viscous/gel forming, readily fermented fibers

E.g., β-glucans from oats and barley, raw guar gum

Soluble fibers dissolve in water, while insoluble fibers do not. Viscous fibers thicken in the presence of water, forming very viscous solutions or even visco-elastic gels. Fermentable fibers are readily metabolized by the gut microbiota (i.e., bacteria that normally colonize the large intestine). Fermentation of fiber results in the formation of short-chain fatty acids (acetate, propionate, and butyrate) and gases (1). Short-chain fatty acids can be absorbed and metabolized to produce energy. Interestingly, the preferred energy source for colonocytes (epithelial cells that line the colon) is butyrate. Fermentation of fiber is estimated to contribute up to 10% of daily energy intake (12). Fibers that are fermentable and can stimulate the growth and/or activity of beneficial gut bacteria are called prebiotic fibers (13). Fibers that are soluble, viscous, and fermentable have been shown to improve glycemic control and to lower blood cholesterol concentration. However, their water-holding capacity is lost when they are fermented in the colon such that they have no laxative effect (see Biological Activities).

Soluble, viscous/gel forming, nonfermented fibers

E.g., psyllium

These fibers can dissolve in water and form viscous gels. They can improve glycemic control and lower blood cholesterol concentration. In addition, they retain their water-holding/gel-forming capacity in the large intestine since they are resistant to fermentation. As a consequence, they can exert a stool-normalizing effect, preventing constipation or softening hard stool as well as firming loose/liquid stool in diarrhea and fecal incontinence (see Biological Activities).

Soluble, nonviscous, readily fermented fibers

E.g., inulin, wheat dextrin, oligosaccharides, resistant starches

Although these fibers can dissolve in water, they cannot provide any health benefits associated with fiber viscosity. They are fully fermented and thus do not exert a laxative effect. They can nonetheless exert a prebiotic effect by influencing the composition of the gut microbiota. *In vitro* studies have shown inulin to selectively stimulate the proliferation of beneficial bacteria and limit the growth of potentially pathogenic bacteria) (see Isolated fibers and supplements) (reviewed in 14). However, no health benefit is currently associated with this fiber-driven prebiotic effect.

Insoluble, poorly fermented fibers

E.g., wheat bran, cellulose, lignin

These fibers do not dissolve in water, do not trap water, and are poorly fermented. Large/coarse fiber particles can have a laxative effect. They can irritate the large intestine mucosa and trigger the secretion of mucus and water, which increases the water content of stools. Small, insoluble fiber particles (e.g., finely ground wheat bran) have no laxative effect and can actually have a constipating effect by adding only to the dry stool mass (see Improving regularity in stool elimination).

Biological Activities

Lowering serum cholesterol

Some, but not all, fibers can improve blood lipid abnormalities observed in conditions like dyslipidemia, overweight/obesity, type 2 diabetes mellitus, and metabolic syndrome. Only supplementation with highly viscous fibers (i.e., gel-forming soluble fibers), such as high molecular weight (MW) β-glucan (found in oat bran), raw guar gum, and psyllium, has been shown to decrease total and LDL-cholesterol concentrations when compared to appropriate controls (e.g., fiber-free supplement, low-fiber supplement, or supplementation with insoluble fiber) (15). A 2009 meta-analysis that combined the results of 21 randomized controlled trials in 1,717 participants with hypercholesterolemia found dose- and time-dependent reductions in total and LDL-cholesterol concentrations with psyllium supplementation (3.0-20.4 g/day for >2 weeks) (16). Additionally, results from two trials showed that, compared to statins alone, combining psyllium and statins resulted in larger reductions in LDL-cholesterol concentrations in individuals with hypercholesterolemia (17). Another more recent meta-analysis of 28 randomized controlled trials examined the cholesterol-lowering effect of psyllium fiber on LDL-cholesterol, non-HDL-cholesterol, and apolipoprotein B (apo B) (18) — non-HDL-cholesterol and apo B appear to better predict cardiovascular events than LDL-cholesterol (19). Supplementation with psyllium at a median dose of 10.2 g/day and for a median of eight weeks to participants with or without hypercholesterolemia reduced LDL-cholesterol by 0.33 mmol/L (28 trials; 1,924 participants), non-HDL-cholesterol by 0.39 mmol/L (27 trials; 1,899 participants), and apo B by 0.05 g/L (9 trials; 895 participants) (18).

Despite considerable heterogeneity across studies, the cholesterol-lowering efficacy of other highly viscous fibers, including β-glucans from oat or barley and glucomannan (a hemicellulose), was also reported in recent meta-analyses of trials conducted by one research team (20-22). The cholesterol-lowering effect of soluble fibers, such as psyllium and β-glucan, is directly linked to their high viscosity. Reduction of the gel-forming capacity of these fibers with pressure and/or heat during processing leads to the loss of their cholesterol lowering capacity (23). Accordingly, low-viscosity soluble fibers (e.g., gum arabic/acacia gum, methylcellulose, low MW β-glucan), nonviscous soluble fermentable fibers (e.g., inulin, fructooligosaccharides, wheat dextrin), and insoluble fibers (e.g., wheat bran) do not decrease serum cholesterol at physiologic levels (15).

Highly viscous fibers can trap bile that is released in the small intestine in response to a meal to assist the digestion and absorption of fatty acids. The main mechanism underlying the cholesterol-lowering effect of these fibers is thus linked to their ability to prevent the reabsorption of bile in the terminal ileum and facilitate its elimination in the stool. In order to maintain sufficient bile for digestion, hepatocytes must increase LDL-cholesterol clearance to synthesize more bile acids as cholesterol is a component of bile (15).

These findings led the FDA to approve health claims in relation to the prevention of heart disease on labels of low cholesterol/saturated fat foods containing ≥0.75 g/serving of β-glucan from whole oat or barley or ≥1.7 g/serving of psyllium (see also Cardiovascular disease) (24).

Improving glycemic control

As with cholesterol lowering, the efficacy of fiber on glycemic control is dependent on viscosity. A 2017 review of 14 randomized controlled trials showed that none of the supplemented soluble, nonviscous, fermentable fibers examined (i.e., inulin, fructooligosaccharide, galactooligosaccharide, and oligofructose) could lead to reductions in postprandial and/or fasting blood glucose concentrations (15). Supplementation with insoluble fiber also failed to improve glycemic control in subjects with elevated fasting blood glucose concentrations (25). In contrast, the capacity of dietary viscous fiber (26, 27) and isolated viscous fibers (28-31) to improve glycemic control has been demonstrated in numerous controlled clinical trials conducted over three decades (15). A 2015 review of the efficacy of psyllium showed evidence of reductions in postprandial blood glucose concentration following a single meal in people with type 2 diabetes mellitus (6 studies) as well as in nondiabetic/euglycemic subjects (11 studies) (32). Supplementation with psyllium also resulted in reductions in postprandial blood insulin concentrations in subjects without type 2 diabetes (6 studies) but not in those with type 2 diabetes (3 studies). Longer-term studies of psyllium supplementation also found reductions in mean fasting glucose (4 studies) and mean glycated hemoglobin (HbA1c; 3 studies) in subjects with type 2 diabetes. Finally, while there was no effect of long-term exposure to psyllium on fasting glucose concentration in healthy individuals with euglycemia (14 studies), the glycemic benefit of psyllium was found to increase proportionally with the increase of baseline fasting glucose concentration (reviewed in 32).

The role of soluble viscous fibers on glycemic control is related to their ability to increase chyme viscosity, thereby slowing the degradation of complex nutrients and allowing the absorption of nutrients, including glucose, along the entire small intestine rather than in the upper small intestine. Absorption of nutrients in the distal ileum has been associated with a reduction in gastric emptying and intestinal transit — through a distal to proximal feedback mechanism — which in turn reduces hunger and food intake (reviewed in 15). Nutrient delivery in the distal ileum also triggers the release of short-lived glucagon-like peptide 1 (GLP-1) into the circulation. GLP-1 improves insulin secretion by pancreatic β-cells in response to glucose absorption and is involved in the regulation of food intake at the central nervous system level (33).

Lowering blood pressure

An analysis of 2004-2014 US National Health and Nutrition Examination Survey (NHANES) data from 18,433 participants found inverse associations between either total, cereal, or vegetable fiber intake and the odds of hypertension (defined according to new 2017 American College of Cardiology/American Heart Association clinical practice guidelines; 34). A 2018 meta-analysis of 22 randomized control trials that examined the effect of isolated soluble fiber supplements or diets enriched with soluble viscous fiber in either normotensive or hypertensive participants found an overall 1.59 mm Hg reduction in systolic blood pressure and 0.39 mm Hg reduction in diastolic blood pressure (35). Further analyses showed that, among all the soluble viscous fiber under examination (β-glucan, guar gum, konjac glucomannan, pectin, and psyllium), only psyllium could reduce systolic blood pressure (mean reduction of 2.39 mm Hg) (35). It is not yet understood how soluble viscous fiber would induce a lowering of blood pressure, but this effect may be indirect and dependent on established benefits of these fiber on other cardiometabolic parameters (see the above sections).

Improving regularity in stool elimination

The benefit of fiber on the regularity with which bulky, soft, easy-to-pass stools are eliminated is best assessed by an increase in stool output and an increase in the water content of stool. There are two mechanisms that support the laxative effects of certain fiber types: (i) large/coarse insoluble fiber (e.g., wheat bran) has an irritating effect on the colonic mucosa, which stimulates the secretion of water and mucus (unlike finely ground wheat bran that has a stool-hardening/constipating effect); and (ii) the presence of soluble viscous, gel-forming fiber (e.g., psyllium) helps stool to resist dehydration in the colon (15). Therefore, only fibers that remain relatively intact during the transit throughout the length of the colon (i.e., that resists bacterial fermentation) and are thus found in the stool can have a potential laxative effect. A 2016 review of fiber interventions conducted by McRorie and Chey (36) examined the potential laxative effect of fermentable fiber; the main findings of this review are summarized in **Table 1**.

Table 1. Interventions Examining the Laxative Effect of Fermentable Fiber (adapted from McRorie and Chey [36])

Fiber	Type of Fiber	Number of Studies	Doses	Laxative Effects	Adverse Effects
β-Glucan, guar gum, xanthan gum	Soluble, viscous, fermentable	5 studies: all conducted in healthy participants; 3 studies with β-glucan and 2 studies (guar gum, xanthan gum)	87-100 g/day (β-glucan) and 15 g/day (guar gum, xanthan gum)	• Stool hardening effect and minimal increase in stool output (β-glucan) • No effect on stool output and stool consistency (guar gum, xanthan gum)	Not reported
Inulin	Soluble, nonviscous, fermentable	11 studies: 3 studies in people with constipation and 8 studies in healthy people	5-20 g/day	• No effect on colonic transit time, stool consistency, stool water content, or stool output	Abdominal pain, bloating, flatulence, and borborygmus (1 study)
Polydextrose	Soluble, nonviscous, fermentable	6 studies: all conducted in healthy participants	8-30 g/day	• No effect on stool output, consistency, bowel movement frequency, or colonic transit time	Flatulence and borborygmus (1 study)
Resistant starch (incl. resistant dextrin)	Soluble, nonviscous, fermentable	6 studies: all conducted in healthy participants	7.5-15 g/day	• Stool hardening effect and reduction in stool output (2 studies) • No effect on consistency, stool water content, stool output, or bowel movement frequency (4 studies)	Not reported

In summary, although the bulk of evidence comes primarily from studies in healthy subjects, supplementation with fermentable fibers appears unlikely to exert a laxative effect in people suffering from constipation (**Table 1**). In contrast, a 2016 meta-analysis of seven randomized controlled trials identified psyllium and nonprebiotics as effectively able to increase stool frequency and improve stool consistency in participants affected by chronic idiopathic constipation (see also Chronic idiopathic constipation) (37) .

Disease Prevention

Observational studies that have identified associations between high-fiber intakes and reductions in chronic disease risk have generally assessed only fiber-rich foods, rather than fiber itself, making it difficult to determine whether the observed benefits are related to fiber or other nutrients and phytochemicals commonly found in fiber-rich foods. In contrast, intervention trials often use isolated fibers to determine whether a specific fiber component has beneficial health effects.

Cardiovascular disease

Prospective cohort studies have consistently reported associations between high intakes of fiber-rich foods and low risks of coronary heart disease (CHD) and total cardiovascular disease (CVD). Three large prospective cohort studies (38-40) found that dietary fiber intakes of approximately 14 g per 1,000 kcal of energy were associated with substantial (16-33%) decreases in the risk of CHD; these results are the basis for the Institute of Medicine's Adequate Intake (AI) recommendation for fiber (see Intake Recommendations) (4). A 2013 meta-analysis of 17 prospective cohort studies found each 7 g/day increase in total dietary fiber intake to be associated with a 9% decrease in risk of coronary or total cardiovascular events (41). The most recent meta-analysis that included 18 prospective studies, with a total of 672,408 participants, found a 7% lower risk of CHD and a 17% lower risk of CHD-related mortality with the highest versus lowest intakes of total dietary fiber (42). Subgroup analyses by type or source of dietary fiber showed evidence of inverse associations between cereal, fruit, or soluble fiber intake and the risk of CHD (42).

The US FDA has approved health claims like the following on the labels of foods containing at least 0.75 g/serving of β-glucan soluble fiber: "Diets low in saturated fat and cholesterol that include at least 3 g/day of β-glucan soluble fiber from either whole oats or barley or a combination of both may reduce the risk of coronary heart disease" (24). Similarly, the FDA has approved health claims on the labels of foods containing at least 1.7 g/serving of psyllium: "Diets low in saturated fat and cholesterol that include at least 7 g/day of soluble fiber from psyllium seed husk may reduce the risk of heart disease" (24).

While the cholesterol-lowering effect of viscous/gel-forming soluble fibers is recognized as a major contributor to the cardioprotective effects of fiber (see Lowering serum cholesterol), other mechanisms are likely to be involved. Findings from pooled analyses of prospective cohort studies found some evidence of an inverse association between the risks of CHD and total CVD and intakes of insoluble fiber (41, 42). In addition, a cross-sectional analysis of 2005-2010 National Health and Nutrition Examination Survey (NHANES) data found dietary fiber intake to be inversely associated with serum LDL-cholesterol concentration, but also with blood pressure, body mass index (BMI), and serum insulin concentration (43). Beneficial effects of fiber-rich diets or isolated fiber consumption on blood glucose and insulin responses and on blood pressure may also likely contribute to observed reductions in CHD risk (see Biological Activities).

Type 2 diabetes mellitus

A 2014 meta-analysis of prospective cohort studies (488,293 participants) found intakes of total fiber (12 studies), cereal fiber (10 studies), fruit fiber (8 studies), and insoluble fiber (3 studies) to be inversely associated with the risk of developing type 2 diabetes mellitus (44). A dose-response data analysis reported a nonlinear relationship between total fiber intake and diabetes risk, with evidence of risk reduction with total fiber intakes ≥25 g/day. A linear dose-response relationship between cereal fiber intake and diabetes risk indicated a 6% reduction in diabetes risk for each 2 g-increment in daily cereal fiber intake. There was no evidence of an inverse association between either vegetable fiber (9 studies) or soluble fiber (3 studies) and the risk of type 2 diabetes (44). Similar findings were reported in another meta-analysis of 18 prospective cohort studies in 617,968 participants (45). Higher versus lower intakes of total fiber were found to be associated with a 15% lower risk of type 2 diabetes (17 studies); the risk of type 2 diabetes was inversely related to the intake of cereal fiber (13 studies) and insoluble fiber (3 studies) but not related to the intake of fruit fiber (11 studies), vegetable fiber (11 studies), or soluble fiber (3 studies) (45). However, only randomized controlled interventions can establish whether there is a link of causality between an exposure (fiber intake) and an outcome (type 2 diabetes). For a discussion of the difference between observational studies and intervention studies, see the article "Epidemiological Studies" in the Spring/Summer LPI 2016 Research Newsletter.

Whole-grain cereals contain insoluble fibers, including cellulose, hemicellulose, and lignin. To date, intervention studies examining the effect of cereal fiber supplementation on the risk of type 2 diabetes are limited (46). In a randomized controlled study of 61 adults with metabolic syndrome, the consumption of a diet based on several whole-grain cereal products for 12 weeks had no effect on fasting plasma concentrations of glucose, insulin, or lipids, or on measures of insulin resistance compared with a refined grain-based diet (47). There was only some weak evidence of an effect of whole-grain cereals on postprandial insulin response (47). A recent 24-month, randomized, double-blind, placebo-controlled trial examined the effect of daily supplementation with 15 g of primarily insoluble fiber on glycemic control in 180 adults with impaired glucose tolerance who were counselled to adopt more healthy lifestyle habits. Insoluble fiber supplementation failed to improve fasting glucose concentration, measures of insulin sensitivity, HbA1c concentration (a marker of glycemic control), as well as glucose and insulin responses after a glucose load compared to placebo (25). Although observational data suggest a protective association of cereal fiber against type 2 diabetes, the current (yet limited) evidence from intervention trials does not support a role for insoluble fiber in glycemic control in individuals at risk of type 2 diabetes.

Fiber-related benefits on glucose homeostasis have been linked to the viscosity of certain soluble fibers (e.g., psyllium, β-glucan, raw guar gum) (see Improving glycemic control). Soluble viscous fibers in cereal, particularly β-glucans, rather than insoluble fiber (and soluble nonviscous fiber), are thus more likely to be involved in a protective effect of cereal intake against type 2 diabetes (48). Apart from fiber, other bioactive compounds in cereal, like magnesium, might contribute to improving glycemic control in people with impaired glucose tolerance (see the article on Magnesium) (49).

The current position of the American Diabetes Association is to encourage people at risk of type 2 diabetes to achieve the daily Adequate Intake (AI) of 14 g/1,000 kcal for dietary fiber (see Intake Recommendations) (50, 51). Adherence to a Mediterranean-style diet, the composition of which intends to meet the AI for fiber, has been associated with a lower risk of developing type 2 diabetes (52, 53).

Metabolic syndrome

Metabolic syndrome is estimated to affect nearly 35% of US adults and half of those older than 60 years (54). The term metabolic syndrome refers to a cluster of metabolic disorders that increase the risk of cardiovascular disease and type 2 diabetes mellitus. The diagnosis in an individual is based on the presence at once of at least three of the following metabolic risk factors: abdominal obesity, dyslipidemia, hypertension, impaired glucose tolerance/insulin resistance, and decreased blood HDL-cholesterol concentration. Two recent meta-analyses of observational studies have reported an inverse association between total fiber intake and odds of metabolic syndrome in cross-sectional studies but not in prospective cohort studies (55, 56).

Cancer

Numerous observational studies have examined the relationship between consumption of fiber and risk of cancer at various sites. A 2014 review compiled published analyses of data from the large, multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort (>500,000 participants). This umbrella review reported evidence of inverse associations between higher versus lower daily total fiber intakes (≥28.5 g/day versus ≤16.4 g/day) and the risk of colorectal, liver, and breast cancers (57). Total fiber intakes were not associated with the risk of cancer at other sites, i.e., the biliary tract, endometrium, prostate, kidney, or bladder. In addition, further analyses suggested that the consumption of cereal fiber was inversely related to the risk of colorectal, stomach, and liver cancers, and vegetable fiber intake was inversely associated with breast cancer. Yet, associations between the consumption of specific fiber types were not examined in relation to the risk of endometrial, kidney, or bladder cancer in EPIC participants (57).

Pooling information from individual observational studies can be helpful to draw conclusions regarding the potential associations between dietary fiber consumption and cancer risk. Results from the most recent meta-analyses of observational studies are reported in **Table 2**.

Table 2. Dietary Fiber Intake and Cancer Risk: Meta-analyses of Observational Studies

Type of Cancer	Type of Observational Studies	Risk Ratio [RR] or Odds Ratio [OR]* (95% Confidence Interval)	Risk Ratio [RR] in Subgroup Analyses (e.g., by fiber type, study type, and cancer subtype)	References
Breast cancer	16 prospective cohort studies	RR: 0.93 (0.89-0.98)	RR: 0.95 (0.86-1.06) in studies reporting on fruit fiber RR: 0.99 (0.92-1.07) in studies reporting on vegetable fiber RR : 0.96 (0.90-1.02) in studies reporting on cereal fiber RR: 0.91 (0.84-0.99) in studies reporting on soluble fiber RR: 0.95 (0.89-1.02) in studies reporting on insoluble fiber	Aune et al. (2012) (75)
	20 prospective cohort and 4 case-control studies	RR: 0.88 (0.83-0.93)	RR: 0.91 (0.87-0.95) in cohort studies only RR: 0.75 (0.47-1.02) in case-control studies only	Chen et al. (2016) (76)
Colorectal adenoma	4 prospective cohort and 16 case-control studies	RR: 0.72 (0.63-0.83)	RR: 0.84 (0.76-0.94) in studies reporting on fruit fiber RR: 0.93 (0.84-1.04) in studies reporting on vegetable fiber RR : 0.76 (0.62-0.92) in studies reporting on cereal fiber RR: 0.92 (0.76-1.10) in cohort studies only RR: 0.66 (0.56-0.77) in case-control studies only	Ben et al. (2014) (58)
Colorectal cancer	11 prospective cohort studies	RR: 0.86 (0.78-0.95) for proximal colorectal cancer	RR: 0.93 (0.72-1.14) in women only RR: 0.79 (0.71-0.87) in men only	Ma et al. (2018) (60)
		RR: 0.79 (0.71-0.87) for distal colorectal cancer	RR: 0.70 (0.52-0.87) in women only RR: 0.85 (0.74-0.95) in men only	
	13 prospective cohort and 8 case-control studies	RR: 0.74 (0.67-0.84)	RR: 0.81 (0.74-0.89) in cohort studies only RR: 0.58 (0.50-0.68) in case-control studies only	Gianfredi et al. (2018) (59)
Endometrial cancer	3 prospective cohort and 11 case-control studies	RR: 0.86 (0.73-1.02)	RR: 1.22 (1.00-1.49) in cohort studies only OR: 0.76 (0.64-0.89) in case-control studies only RR: 1.26 (1.03-1.52) in studies reporting on cereal fiber OR: 0.74 (0.58-0.94) in studies reporting on vegetable fiber	Chen et al. (2018) (83)
Esophageal cancer	9 case-control studies		OR: 0.66 (0.44-0.98) for esophageal adenocarcinoma OR: 0.61 (0.31-1.20) for esophageal squamous cell carcinoma	Coleman et al. (2013) (84)
	15 case-control studies	OR: 0.52 (0.43-0.64)	OR: 0.42 (0.29-0.61) for Barrett's esophagus (precancerous lesions) OR: 0.56 (0.37-0.67) for esophageal adenocarcinoma OR: 0.53 (0.31-0.90) for esophageal squamous cell carcinoma OR: 0.73 (0.48-1.12) in studies reporting on fruit fiber OR: 0.61 (0.45-0.83) in studies reporting on vegetable fiber OR : 0.81 (0.61-1.07) in studies reporting on cereal fiber OR: 0.85 (0.65-1.11) in studies reporting on grain fiber OR: 0.40 (0.20-0.78) in studies reporting on soluble fiber OR: 0.37 (0.18-0.75) in studies reporting on insoluble fiber	Sun et al. (2017) (85)
Gastric cancer	2 prospective cohort and 19 case-control studies	OR: 0.58 (0.49-0.67)	OR: 0.67 (0.46-0.99) in studies reporting on fruit fiber OR: 0.72 (0.57-0.90) in studies reporting on vegetable fiber OR: 0.58 (0.41-0.82) in studies reporting on cereal fiber OR: 0.41 (0.32-0.52) in studies reporting on soluble fiber OR: 0.42 (0.34-0.52) in studies reporting on insoluble fiber	Zhang et al. (2013) (86)
Ovarian cancer	5 prospective cohort and 14 case-control studies	RR: 0.70 (0.57-0.87)	RR: 0.97 (0.85-1.12) in cohort studies RR: 0.62 (0.47-0.82) in case-control studies	Xu et al. (2018) (87)
	4 prospective cohort and 13 case-control studies	RR: 0.76 (0.70-0.82)	RR: 0.76 (0.63-0.92) in cohort studies RR: 0.75 (0.68-0.83) in case-control studies	Huang et al. (2018) (88)
Pancreatic cancer	1 prospective cohort and 13 case-control studies	OR: 0.52 (0.43-0.63)	OR: 1.01 (0.59-1.73) in the cohort study OR: 0.54 (0.44-0.67) in case-control studies	Wang et al. (2015)** (89)
	1 prospective cohort and 13 case-control studies	OR: 0.52 (0.44-0.61)	OR: 0.66 (0.51-0.80) in studies reporting on soluble fiber OR: 0.65 (0.44-0.87) in studies reporting on insoluble fiber	Mao et al. (2017)** (90)
Prostate cancer	5 prospective cohort and 12 case-control studies	OR: 0.89 (0.77-1.01)	OR: 0.94 (0.77-1.11) in cohort studies OR: 0.82 (0.68-0.96) in case-control studies OR: 0.92 (0.81-1.03) in studies reporting on fruit fiber OR: 0.87 (0.53-1.21) in studies reporting on vegetable fiber OR: 1.05 (0.94-1.16) in studies reporting on cereal fiber OR: 0.87 (0.52-1.22) in studies reporting on soluble fiber OR: 0.80 (0.46-1.13) in studies reporting on insoluble fiber	Sheng et al. (2015) (91)
	5 prospective cohort and 11 case-control studies	RR: 0.94 (0.85-1.05)	OR: 0.99 (0.87-1.14) in cohort studies OR: 0.89 (0.75-1.06) in case-control studies	Wang et al. (2015) (92)
Renal cell carcinoma	2 prospective cohort and 4 case-control studies	RR: 0.84 (0.74-0.96)	OR: 0.88 (0.69-1.12) in cohort studies OR: 0.82 (0.68-1.00) in case-control studies OR: 0.92 (0.80-1.05) in studies reporting on fruit fiber OR: 0.70 (0.49-1.00) in studies reporting on vegetable fiber OR: 1.04 (0.91-1.18) in studies reporting on cereal fiber OR: 0.83 (0.70-0.97) in studies reporting on soluble fiber OR: 0.81 (0.69-0.94) in studies reporting on insoluble fiber	Huang et al. (2015) (93)
*for the highest versus lowest level of fiber intake (unless otherwise specified) **both meta-analyses identified the same 14 observational studies				

Colorectal cancer

Three most recent meta-analyses of observational studies have reported evidence of an inverse association between fiber intake and risk of colorectal cancer (see **Table 2**) (58-60). A recent review that included earlier meta-analyses reached a similar conclusion (61).

Several mechanisms have been proposed to explain why consuming fiber can have a protective effect against colorectal cancer. First, the presence of insoluble, coarse fiber can increase stool bulk thereby promoting the fecal excretion of carcinogens like nitrosamines (62). Fiber can also reduce exposure of the gut mucosa to carcinogens by shortening transit time (62). Secondly, fiber consumption influences the composition of the gut microbiota. *In vitro* studies have shown inulin to selectively stimulate the proliferation of beneficial bacteria while limiting the growth of potentially pathogenic bacteria (reviewed in 14). Gut bacterial imbalance (dysbiosis) has been associated with the incidence of several conditions, including colorectal cancer (63). The major health benefits conferred by the consumption of fiber are thus likely mediated by the bacteria the fiber contributes to feed. Depending on the physicochemical characteristics of fiber, some fiber, like inulin, can be fermented by colonic bacteria and lead to the formation of short-chain fatty acids, namely acetate, propionate, and butyrate. These short-chain fatty acids have been found to protect against gastrointestinal bacterial pathogens (64) and to display anti-inflammatory and anti-carcinogenic actions (65, 66).

A few controlled clinical trials have examined the effect of fiber consumption on the recurrence of colorectal adenomas (precancerous polyps), but none have been conducted in the last two decades. These trials examined the effect of wheat bran fiber (67-71), psyllium (72), and a high-fiber diet (73) on the risk of adenomas in participants with a history of adenomas. A 2017 meta-analysis of these trials found no difference between intervention and control groups in the number of participants with at least one new adenomatous polyp during the follow-up period (2-8 years), regardless of the type of fiber intervention (74).

Breast cancer

A review of four meta-analyses of observational studies reported substantial evidence of an inverse association between dietary fiber intake and breast cancer risk (61). The two most recent meta-analyses of prospective cohort studies found dietary fiber intake to be associated with a 7%-9% lower risk of breast cancer (**Table 2**) (75, 76). Prolonged exposure to estrogens has been associated with an increased risk of breast cancer (77). As mentioned in the previous section, several mechanisms might support the potential protective effect of dietary fiber against cancer, including breast cancer. The results of small, short-term intervention trials in premenopausal and postmenopausal women suggested that a low-fat (10-25% of total energy), high-fiber (25-40 g/day) diet could decrease circulating estrogen concentrations by increasing the excretion of estrogens and by promoting the metabolism of estrogens to less estrogenic forms (78, 79). Estrogens are conjugated in the liver and excreted within the bile into the gastrointestinal lumen; they are then de-conjugated by bacterial β-glucuronidase, re-absorbed as free estrogens through the enterohepatic circulation, and delivered to different organs and tissues like the breast.

Dietary fiber might interfere with estrogen reabsorption by reducing β-glucoronidase activity (80). Alterations in gut bacteria composition have also been reported in women with breast cancer and might contribute to increased estrogen metabolism and absorption, resulting in higher circulating estrogen concentrations (81). However, it is not known whether fiber-associated effects on endogenous estrogen concentrations have a clinically significant impact on breast cancer risk (4). Finally, a healthy microbiota might also promote the degradation of plant-derived molecules other than fiber, such as lignans, which are precursors of metabolites with anti-estrogenic activities (82).

Other cancer sites

A review of the most recent meta-analyses of observational studies suggests that dietary fiber consumption is inversely associated with the risk of cancer of the esophagus (84, 85), stomach (86), pancreas (89, 90), and ovaries (see **Table 2**) (87, 88). The evidence linking fiber intake and esophageal cancer was exclusively based on observations from case-control studies, and for the other cancer sites, the evidence is primarily derived from case-control studies (**Table 2**). It is important to note that the evidence of an inverse association between fiber intake and risk of ovarian cancer (2 meta-analyses) was observed in case-control but not in prospective cohort studies (**Table 2**). Additionally, there was no evidence of an association between fiber intake and risk of endometrial cancer (1 meta-analysis; 83), prostate cancer (2 meta-analyses; 91, 92), or renal cell carcinoma (1 meta-analysis; 93) (**Table 2**). At present, evidence from randomized controlled trials of a causal relationship between fiber intake and risk of any cancer is lacking.

Of note, a recent study in a mouse model presenting a dysbiotic microbiota characterized by an increase in fiber-fermenting bacteria showed that the consumption of an obesogenic, high-fat diet enriched with soluble fiber could cause icteric hepatocarcinoma (94). Such findings suggest that a prolonged consumption of fermentable fiber may have detrimental consequences in contexts of dysbiosis. No such observations were found when insoluble fiber were substituted for soluble fiber (94).

Diarrhea associated with enteral nutrition

Gastrointestinal disorders associated with enteral nutrition prolong the time to recovery. A 2015 meta-analysis of 14 intervention studies found that fiber-enriched enteral formulas and/or fiber supplements reduced the overall incidence of diarrhea in patients requiring enteral nutrition (95). There was no reduction in incidental diarrhea when the analysis was restricted to studies that used prebiotic fiber (i.e., fermentable fiber influencing microbiota composition). Subgroup analyses also showed a benefit of fiber in non-critically ill patients but not in critically ill patients (95).

Fecal incontinence

A prospective cohort study that followed nearly 60,000 older women for four years found that the highest versus lowest level of fiber intake (mean, 25 g/day versus 13.5 g/day) was associated with a 17% lower risk of developing fecal incontinence (defined here as an incontinence episode of liquid or solid stool at least once a month) (96). A limited number of studies have also examined whether fiber supplementation might help treat established fecal incontinence. In one placebo-controlled trial, 206 subjects suffering from fecal incontinence were randomized for 32 days to receive fibers with different degrees of fermentability: gum arabic (on average, 16.6 g/day; highly fermentable), sodium carboxymethylcellulose (16.2 g/day; partially fermentable), and psyllium (14.6 g/day; poorly fermentable) (97). The frequency of fecal incontinence increased with sodium carboxymethylcellulose but decreased with gum arabic and psyllium compared to placebo. Stool consistency and amount did not differ among groups (97). A randomized, cross-over trial in 80 community-dwelling participants with at least one fecal incontinence episode per week found that the reduction in fecal incontinence frequency and severity with psyllium supplementation was equivalent to that observed with antidiarrheal drug loperamide (Imodium) (98).

Weight control

It has been suggested that higher fiber intakes could help maintain weight or promote weight loss by increasing satiation (causing meal termination) and/or extending the feeling of fullness after a meal (satiety). Several mechanisms have been proposed to explain the potential satiating effect of fibers and the subsequent reduction in food intake. The presence of fiber in food may indirectly stimulate the production of hormones involved in the regulation of appetite in particular through (i) increasing the processing time in the mouth due to increased efforts required to masticate large particles containing fibers, and/or (ii) increasing the duration of stomach distention due to a lower rate of gastric emptying, and/or (iii) increasing the colonic production of short-chain fatty acids that can bind to receptors present on gut endocrine cells (reviewed in 99). Adverse effects like gas production and bloating observed with the supplementation of isolated fibers (e.g., wheat dextrin) might also reduce hunger and increase satiety.

A 2013 review of 44 randomized controlled trials found that β-glucans from oat or barley, lupin kernel fiber, whole grain rye, rye bran, and a mixed high-fiber diet could enhance satiety, whereas psyllium, whole grain barley, whole grain buckwheat, resistant starch, and wheat bran had no benefit or even reduced measures of satiety (100). However, for many types of fiber examined, results from interventions were mixed, some showing a positive effect on satiety, and others showing no effect. Additionally, there seemed to be no relationship between the physicochemical properties of fiber (i.e., solubility, viscosity, fermentability) and evidence of efficacy. For example, among soluble viscous fibers, β-glucans appeared to enhance satiety, but pectin or psyllium did not. Similarly, among fermentable fibers, β-glucans enhanced satiety, but guar gum, inulin, fructooligosaccharides, and resistant starch did not. Finally, a positive effect of fiber on satiety was not consistently associated with a reduction in food intake (100).

A 2011 systematic review of 61 randomized controlled studies examined the effect of different fiber types on body weight (101). This analysis found that dextrins and marine polysaccharides reduced body weight in all the studies, while chitosan, arabinoxylans, and fructans reduced body weight in at least two-thirds of the studies. Average weight reductions were greatest for the fructans and marine polysaccharides groups (~1.3 kg or 2.8 lb/4 weeks for a 79 kg person in both groups). For all fiber types combined, however, the average weight reduction was only 0.3 kg (0.7 lb) per 4 weeks for a 79-kg person (101). A few randomized controlled trials in overweight or obese subjects suggested that psyllium supplementation may influence body composition and/or promote weight loss (reviewed in 102). In one randomized, placebo-controlled trial in 159 Australian with body mass indices (BMI) ≥25 kg/m^2, psyllium (5 g/day) reduced waist circumference, waist-to-hip ratio, and body fat percentage, and increased the percentage of lean mass after 3, 6, and 12 months (103). Psyllium appeared to transiently reduce body weight at 3 and 6 months, yet there was no difference in body weight between psyllium and placebo at the end of the intervention (12 months) (103).

More research needs to be conducted in order to clarify which types of fiber might play a role in appetite regulation and weight management (99).

Mortality

Several prospective cohort studies have examined dietary fiber intake in relation to all-cause and cause-specific mortality. A 2015 report from the NIH-AARP Diet and Health Study, which followed 364,442 older adults for an average of 14 years, found that men and women in the highest versus lowest quintile of dietary fiber intake (mean, 10.2 g/day versus 2.0 g/day) had lower risks of all-cause mortality (-19%) and mortality from cardiovascular disease (-20%), cancer (-15%), diabetes mellitus (-34%), and respiratory diseases (-21%) (104). Another prospective study that made use of data collected from 15,740 participants in the US National Health and Nutrition Examination Survey (NHANES) 1988-1994 found a 13% lower risk of all-cause mortality in subjects with total fiber intake between 14.5 g/day and 22.1 g/day — but not in those with higher intake (>22.1 g/day) — compared to those with fiber intake less than 9.3 g/day, over a mean follow-up period of 13.7 years (105). No associations were found between intakes of either insoluble or soluble fiber and all-cause mortality (105).

A meta-analysis of prospective cohort studies published before 2013, which included a total of 1,752,848 participants followed for a mean 12.4 years, found higher versus lower total fiber intake to be associated with lower risks of all-cause mortality (-23%; 9 studies), cancer-related mortality (-17%; 5 studies), and cardiovascular disease-related mortality (-23%; 16 studies) (106). Another meta-analysis identified 14 prospective cohort studies that examined cereal fiber intake in relation to mortality (107). Participants in the highest versus lowest quartile of cereal fiber intake had lower risks of all-cause mortality (-19%; 3 studies), cardiovascular disease-related mortality (-18%; 10 studies), and cancer-related mortality (-25%; 2 studies) (107).

Disease Treatment

Diabetes mellitus

A 2004 meta-analysis that combined the results of 23 clinical trials in patients with type 1 or type 2 diabetes mellitus found that high-fiber diets (≥20 g/1,000 kcal) lowered postprandial blood glucose concentrations by 13%-21%, serum LDL cholesterol concentrations by 8%-16%, and serum triglyceride concentrations by 8%-13% when compared with low-fiber diets (<10 g/1,000 kcal) (108). Based on the evidence from this meta-analysis, the authors recommended a dietary fiber intake of 25-50 g/day (15-25 g/1,000 kcal) for individuals with diabetes, which is slightly higher than recommendations for the general public (14 g/1,000 kcal) (4). However, recommendations from the American Diabetes Association and the Academy of Nutrition and Dietetics to people with diabetes are similar to those prescribed for the population as a whole (50, 109).

Adhering to one of the USDA's healthy dietary patterns, like the Mediterranean-style diet (which is rich in fruit, vegetables, and whole grains), would contribute to meeting the daily intake recommendation for total fiber (see Intake Recommendations) (110). A 2015 meta-analysis of nine randomized controlled trials in a total of 1,178 participants with type 2 diabetes showed evidence of body weight loss and improvements in glycemic control and blood lipid profile with the consumption of a Mediterranean-style diet compared to a control diet (111).

Numerous controlled clinical trials have shown that supplementation with soluble viscous fibers improves markers of glycemic control in people who have type 2 diabetes mellitus. A meta-analysis of 28 trials in 1,394 adults with type 2 diabetes found reductions in HbA1c concentration (20 trials), fasting glucose concentration (28 trials), and insulin resistance (11 trials) with soluble viscous fiber supplementation (median doses of 10.5-15 g/day for 6-8 weeks) (112). Another meta-analysis of 35 trials showed that the effect of psyllium varied with baseline fasting glucose concentration: psyllium supplementation had no effect on markers of glycemic control in euglycemic participants but showed a modest benefit in subjects with impaired glucose tolerance, and a greater effect in those with overt type 2 diabetes (see also Biological Activities) (32).

A small randomized uncontrolled trial in 20 healthy participants suggested that supplemental wheat dextrin, which is partially absorbed as sugar in the small intestine, could increase fasting glucose concentration into the prediabetes range after one month of supplementation (113). Since there is little evidence from clinical trials that increasing nonviscous fiber alone is beneficial (114), individuals with diabetes should preferably increase fiber intake from sources of soluble viscous fibers, such as oats and barley (β-glucans), vegetables, beans, and legumes (108).

Gastrointestinal disorders

Chronic idiopathic constipation

Only insoluble fibers and soluble viscous fibers that resist bacterial fermentation in the colon have a potential laxative effect (see Improving regularity in stool elimination) (15). The prevalence of chronic constipation is higher among people with diabetes mellitus, in women during pregnancy and after delivery, or in older people. The management of constipation in these patients is usually similar to the management in the rest of the population, although the etiology might be different. Bulk-forming laxatives, including psyllium, bran, and methylcellulose, are commonly recommended to improve stool regularity in patients with diabetes mellitus (115). However, there is no evidence that methylcellulose and bran are efficacious in patients with constipation (116). In these patients, psyllium is also recognized to improve glycemic control (see Diabetes mellitus). There is a need for good quality, randomized, double-blind, controlled trials to examine the effect of fiber supplementation in the treatment of constipation in older adults in long-term care (117) or in pregnant women and new mothers (118, 119).

The American College of Gastroenterology recognizes the efficacy of soluble fiber in the treatment of chronic idiopathic constipation. It also recognizes that the evidence from observational studies is mixed, as constipation is associated with low-fiber diets in some, but not all, studies (120). It recommends a gradual increase in fiber intake, in particular to limit the potential adverse effects associated with the intake of insoluble fiber, i.e., bloating, distension, flatulence, and cramping (121).

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional disorder of the intestines, characterized by episodes of abdominal pain or discomfort associated with altered gut mobility and changes in bowel habits (i.e., with constipation, diarrhea, or both) (122). Although the pathophysiology of IBS remains unclear, certain food components have been recognized as a cause for symptoms of IBS. Dietary restriction of highly fermentable, soluble, short-chain carbohydrates, identified as FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) and including some dietary fibers (e.g., fructans, galactooligosaccharides), has been found to relieve IBS symptoms, including abdominal pain/discomfort, abdominal bloating/distension, and flatulence (123). On the other hand, soluble, poorly fermentable, long-chain carbohydrate fiber types may improve the symptoms related to excessive gas production. Two meta-analyses of randomized controlled trials and cross-over studies found a beneficial effect of fiber that was limited to soluble fiber, primarily psyllium (124, 125). Accordingly, the American College of Gastroenterology recognizes that soluble fiber like psyllium can provide overall symptom relief in IBS, while insoluble fiber (e.g., wheat bran) can cause bloating and abdominal discomfort (121). More research is needed to document the effect of specific soluble fibers, considering physicochemical properties (viscosity and fermentability), doses, and duration of supplementation, and to provide stronger recommendations to individuals diagnosed with IBS (125). Future trials should also consider subjects with all of the IBS types, i.e., constipation-predominant, diarrhea-predominant, and mixed-diarrhea-and-constipation IBS.

Diverticular disease

Diverticular disease or diverticulosis is a rather common gastrointestinal condition in Western countries characterized by the formation of small pouches (diverticula) in the colon (126). Acute inflammation or infection of diverticula — known as diverticulitis — occurs in about 10%-25% of all symptomatic cases of diverticulosis and is caused by the irritation of the mucosa by fecalith obstructing diverticula. Complications of diverticulitis include abscesses, fistulas, obstruction, and perforation (126). The etiology of diverticulosis is thought to be multifactorial, involving both genetic and environmental risk factors. Despite little supporting evidence, it has been proposed that low fiber intakes that characterize Western diets might contribute to increasing the risk of diverticulosis (127, 128). This low-fiber hypothesis is disputed. In particular, a 2012 cross-sectional study of 2,104 adults found higher odds of diverticula (assessed by colonoscopy) among participants in the highest versus lowest quartile of fiber intake, measured by food frequency questionnaires (129).

A 2017 review identified interventions — published over four decades — that examined the effect of dietary or supplemental fiber on the reduction of abdominal pain in patients suffering from symptomatic uncomplicated diverticular disease (SUDD), as well as on the risk of acute diverticulitis (130). However, a meta-analysis could not be conducted nor any conclusion provided regarding the efficacy of fiber in the treatment of SUDD due to the very poor quality of the studies and their substantial heterogeneity in terms of study design and quantity and quality of fiber types used (130). Another recent review of the literature focused on the effect of fiber-restricted diets in the management of acute uncomplicated diverticulitis (131). Based on the review of three randomized controlled trials and two observational studies, the authors found a reduced length of hospital stay with non-restricted diets compared to restricted diets, but no difference regarding the incidence of treatment failure (i.e., the risk of no clinical improvement with therapy and the development of complications) and the risk of post-discharge reoccurrence of diverticulitis. While there appears to be no clinical benefit in restricting fiber intake in subjects with uncomplicated diverticulitis, the quality of the studies was once again deemed to be very low (131).

Despite the lack of high-quality evidence regarding the potential benefit of fiber in the management of diverticular disease, many national guidelines recommend the use of high-fiber diets in patients with SUDD and for the prevention of diverticulitis (132, 133).

Hemorrhoids

A limited number of interventions have examined the effect of fiber supplementation in subjects with symptomatic hemorrhoids. A randomized controlled trial in 67 participants found that supplementation with psyllium (7 g/day for 6 weeks) improved stool consistency and regularity, reduced the use of laxatives, and increased the quality of life compared to a placebo (134). Another randomized controlled trial in 50 patients with hemorrhoidal prolapse (grades II-IV) and rectal bleeding showed that psyllium supplementation (11.6 g/day for 40 days) reduced the number of bleeding episodes and the number of congested hemorrhoidal cushions but had no effect on the degree of prolapse (135). Finally, a more recent uncontrolled intervention in 102 individuals with advanced hemorrhoids (grades II-IV) examined the effect of counseling patients to follow a therapy meant to improve defecatory habits and involving an increase of psyllium intake to 20 g/day-25 g/day. A follow-up for a median 40 months suggested that psyllium supplementation might help halt the progression of hemorrhoidal prolapse and reduce the number of bleeding episodes (136).

Sources

Food sources

An analysis of the 2009-2010 US National Health and Nutrition Examination Survey (NHANES) data reported average dietary fiber intakes of 13.6 g/day in children and adolescents and 17 g/day in adults—well below recommended intake levels (see Intake Recommendations) (137). Fiber is identified as a shortfall nutrient of public health concern in the 2010-2015 Dietary Guidelines for Americans (51).

Good sources of dietary fiber include legumes, nuts, whole grains, bran products, fruit, and nonstarchy vegetables. Legumes (e.g., dry beans and peas), nuts, seeds, and whole grains are generally more concentrated sources of fiber than fruit and vegetables (138). These higher fiber foods are currently underconsumed, contributing to only about 6% of total dietary fiber intake (137). Although refined grains are often perceived as being poor sources of fiber, they can provide as much fiber as either fruit or vegetables when comparable serving sizes are consumed (138). In addition, not all whole grains are good sources of fiber, yet they provide key micronutrients and phytochemicals that contribute to the health benefit associated with whole grain consumption (see the article on Whole Grains) (12).

All plant-based foods contain a mixture of soluble and insoluble fiber (138). Bran flaxseed, oat cereal, legumes, nuts, fruit, and vegetables are good sources of soluble viscous and nonviscous fiber. Wheat bran, brown rice, barley, cabbage, celery, and whole grains are rich sources of insoluble fiber. The total fiber content of some fiber-rich foods is presented in **Table 3**. Some strategies for increasing dietary fiber intake include increasing fruit and nonstarchy vegetable intake, increasing intake of legumes, eating whole-grain cereal or oatmeal for breakfast, substituting whole grains for refined grains, and substituting nuts or popcorn for less healthy snacks. For more information about the fiber content of specific foods, search USDA's FoodData Central database.

Table 3. Some Food Sources of Dietary Fiber

Food	Serving	Fiber (g)
Legumes		
Navy beans, cooked, boiled	½ cup	9.6
Split peas, cooked, boiled	½ cup	8.1
Lentils, cooked, boiled	½ cup	7.8
Refried beans, canned	½ cup	5.7
Kidney beans, canned	½ cup	5.5
Cereal and grains		
All-bran (wheat) cereal	½ cup	19.5
Oats	½ cup	4.1
Bulgur, cooked	½ cup	4.1
Cereal, instant oatmeal	½ cup	4.0
Pearled barley, cooked	½ cup	3.0
Oat bran, cooked	½ cup	2.8
Quinoa, cooked	½ cup	2.6
Rice, long-grain, brown, cooked	½ cup	1.6
Vegetables		
Winter squash, butternut, cooked, baked	1 cup	6.6
Artichoke hearts, cooked	½ cup	4.8
Spinach, frozen, cooked	½ cup	3.5
Mushrooms, white, cooked from fresh	1 cup	3.4
Brussel sprouts, frozen, cooked	½ cup	3.2
Fruit		
Plums, dried (prunes), uncooked	½ cup, pitted	6.2
Guava, fresh	½ cup	4.5
Pear	1 small pear	4.6
Asian pear	1 small pear	4.4
Raspberries, fresh	½ cup	4.0
Blackberries, fresh	½ cup	3.8
Plums, fresh	2 plums	1.8
Nuts and Seeds		
Almonds	1 ounce (23 kernels)	3.5
Pistachios	1 ounce (49 kernels)	3.0
Pine nuts	1 ounce	3.0
Hazelnuts	1 ounce (21 kernels)	2.7
Pecans	1 ounce (19 halves)	2.7
Peanuts	1 ounce	2.4

Isolated fibers and supplements

β-Glucans

β-Glucans are viscous, easily fermented, soluble fibers found naturally in oats, barley, mushrooms, yeast, bacteria, and algae. β-Glucans extracted from oats, mushrooms, and yeast are available in a variety of nutritional supplements without a prescription.

Glucomannan

Glucomannan, sometimes called konjac mannan, is classified as a soluble fiber isolated from konjac flour, which is derived from the plant *Amorphophallus konjac*. Glucomannan is available as powder and in capsules, which should be taken with plenty of liquids (8). Glucomannan forms gels that are firmer than regular gelatin products (e.g., "jello") and do no melt in the mouth. The FDA has banned gel candies containing glucomannan (e.g., "mini-cup jelly products") because of their potential to cause choking (139).

Pectin

Pectins are readily fermented soluble viscous fibers, most often extracted from citrus peels and apple pulp. Pectins are widely used as gelling agents in food but are also available as dietary supplements without a prescription (8).

Inulins and oligofructose

Inulins and oligofructose, extracted from chicory root or synthesized from sucrose, are used as food additives (9). Isolated inulin is added to replace fat in products like salad dressing, while sweet-tasting oligofructose is added to products like fruit yogurts and desserts. Inulins and oligofructose are highly fermentable fibers that are also classified as prebiotics because of their ability to stimulate the growth of potentially beneficial *Bifidobacteria* species in the human colon (140). Encouraging the growth of *Bifidobacteria* might promote intestinal health by suppressing the growth of pathogenic bacteria known to cause diarrhea or by enhancing the immune response (141). Although a number of dietary supplements containing inulins and oligofructose are marketed as prebiotics, the health benefits of prebiotics have not yet been convincingly demonstrated in humans (11, 142).

Guar gum

Raw guar gum is a viscous, fermentable fiber derived from the Indian guar or cluster bean (4). It is used as a thickener or emulsifier in many food products. Dietary supplements containing guar gum have been marketed as weight-loss aids, but there is no evidence of their efficacy (143). Unlike guar gum, partially hydrolyzed guar gum is nonviscous and therefore does not exhibit the biological activities of guar gum (i.e., it has no effect on serum cholesterol and glycemic control) (see Biological Activities).

Psyllium

Psyllium, a viscous, soluble, gel-forming fiber isolated from psyllium seed husks, is available without a prescription in laxatives, ready-to-eat cereal, and dietary supplements (8). Psyllium is proven to be efficacious to lower serum cholesterol and improve glycemic control (see Biological Activities). Because it also normalizes stool form, psyllium is the only fiber recommended by the American College of Gastroenterology to treat chronic constipation and irritable bowel syndrome (see Gastrointestinal disorders).

Chitosan

Chitosan is an indigestible glucosamine polymer derived from chitin. Chitosan is available as a dietary supplement without a prescription in the US, being marketed to promote weight loss and lower cholesterol. A 2018 meta-analysis of randomized controlled, clinical trials found a lowering of total and LDL-cholesterol concentrations with chitosan supplementation (0.3-6.75 g/day for 4-24 weeks) and no effect on HDL-cholesterol or triglycerides (144). Another recent pooled analysis of trials found chitosan to be more effective than placebo in promoting weight loss (145).

Note: All fiber supplements should be taken with sufficient fluids. Most clinicians recommend taking fiber supplements with at least 8 ounces (240 mL) of water and consuming a total of at least 64 ounces (~2 liters or 2 quarts) of fluid daily (146, 147).

Safety

Adverse effects

Dietary fiber

Some people experience abdominal cramping, bloating, or gas when they abruptly increase their dietary fiber intake (146, 147). These symptoms can be minimized or avoided by increasing intake of fiber-rich foods gradually and increasing fluid intake to at least 64 oz/day (~2 liters or 2 quarts/day). There have been rare reports of intestinal obstruction related to large intakes of oat bran or wheat bran, primarily in people with impaired intestinal motility or difficulty chewing (148-151). The National Academy of Medicine (formerly, the Institute of Medicine) has not established a tolerable upper intake level (UL) for dietary or functional fiber (4).

Isolated fibers and fiber supplements

Gastrointestinal symptoms: The following fibers have been found to cause gastrointestinal distress, including abdominal cramping, bloating, gas, and diarrhea: guar gum, inulin and oligofructose, fructooligosaccharides, polydextrose, resistant starch, and psyllium (4). It is recommended to gradually introduce a new fiber supplement, not exceeding 3 to 4 g/day the first week, in order to minimize gastrointestinal symptoms (152). In subjects who are constipated, the initiation of a fiber supplement should start once the hard stool is cleared (152). Use of a guar gum-containing supplement for weight loss has been associated with esophageal and small bowel obstruction (153). Additionally, several cases of intestinal obstruction by psyllium have been reported when taken with insufficient fluids or by people with impaired swallowing or gastrointestinal motility (154, 155).

Colorectal adenomas: One randomized controlled trial in patients with a history of colorectal adenomas (precancerous polyps) found that supplementation with 3.5 g/day of psyllium for three years resulted in a significant increase in colorectal adenoma recurrence compared to placebo (see Colorectal cancer) (72).

Allergy and anaphylaxis: Since chitin is isolated from the exoskeletons of crustaceans, such as crabs and lobsters, and chitosan is derived from chitin, people with shellfish allergies should avoid taking chitosan supplements (8). Anaphylaxis has been reported after intravenous (IV) administration of inulin (156), as well as ingestion of margarine containing inulin extracted from chicory (157). Anaphylaxis has also been reported after the ingestion of cereal containing psyllium, and asthma has occasionally been reported in people with occupational exposure to psyllium powder (158).

Drug interactions

Gel-forming fibers (e.g., β-glucan, psyllium, raw guar gum, pectin) have the potential to slow the absorption of drugs if taken at the same time. Psyllium may reduce the absorption of lithium, carbamazepine (Tegretol), digoxin (Lanoxin), and warfarin (Coumadin) when taken at the same time (8). Guar gum may slow the absorption of digoxin, acetaminophen (Tylenol), and bumetanide (Bumex) and decrease the absorption of metformin (Glucophage), penicillin, and some formulations of glyburide (Glynase) when taken at the same time (159). Pectin may decrease the absorption of lovastatin (Mevacor) when taken at the same time (160). Concomitant administration of a kaolin-pectin antidiarrheal suspension has been reported to decrease the absorption of clindamycin, tetracycline, and digoxin, but it is not known whether kaolin, pectin, or both were responsible for the interaction (8). In general, medications should be taken at least one hour before or two hours after fiber supplements and gel-forming dietary fibers (e.g., oatmeal).

Nutrient interactions

The addition of cereal fiber to meals has generally been found to decrease the absorption of iron, zinc, calcium, and magnesium in the same meal, but this effect appears to be related to the phytate present in the cereal fiber rather than the fiber itself (161). In general, dietary fiber as part of a balanced diet has not been found to adversely affect the calcium, magnesium, iron, or zinc status of healthy people at recommended intake levels (4). Evidence from animal studies and limited research in humans suggests that inulin and oligofructose may enhance calcium absorption (162, 163). The addition of pectin and guar gum to a meal significantly reduced the absorption of the carotenoids β-carotene, lycopene, and lutein from that meal (164, 165).

Intake Recommendations

The Adequate Intake (AI) for total fiber

The Adequate Intake (AI) recommendations for total fiber intake, set by the Food and Nutrition Board of the Institute of Medicine, are based on the findings of several large prospective cohort studies that dietary fiber intakes of approximately 14 g for every 1,000 calories (kcal) consumed were associated with significant reductions in the risk of coronary heart disease (CHD). The FDA approved specific health claims related to the cardioprotective effects of two soluble, gel-forming fibers only: β-glucan and psyllium (see Disease Prevention). For adults who are 50 years of age and younger, the AI recommendation for total fiber intake is 38 g/day for men and 25 g/day for women. For adults over 50 years of age, the recommendation is 30 g/day for men and 21 g/day for women. The AI recommendations for males and females of all ages are presented in **Table 4** (4).

Table 4. Adequate Intake (AI) for Total Fiber

Life Stage	Age	Males (g/day)	Females (g/day)
Infants	0-6 months	ND*	ND
Infants	7-12 months	ND	ND
Children	1-3 years	19	19
Children	4-8 years	25	25
Children	9-13 years	31	26
Adolescents	14-18 years	38	26
Adults	19-50 years	38	25

Adults	51 years and older	30	21
Pregnancy	all ages	-	28
Breast-feeding	all ages	-	29
*Not determined			

Some suggestions for increasing fiber intake

- Eat at least five servings of fruit and vegetables daily (see the article on Fruit and Vegetables).
- Substitute whole grains for refined grains (see the article on Whole Grains).
- Eat oatmeal, whole-grain cereal, or bran cereal for breakfast.
- Eat beans, split peas, or lentils at least once weekly (see the article on Legumes).
- Substitute nuts or popcorn for less healthful snacks like potato chips or candy (see the article on Nuts).

Adopting one of the USDA healthy dietary patterns (i.e., healthy US-style, healthy Mediterranean-style, and healthy vegetarian dietary patterns) recommended in the 2015-2020 Dietary Guidelines for Americans will help meet the recommendations for total fiber intake (110). Fruit, vegetables, and whole grains available in the USDA dietary patterns contribute nearly 90% of the recommended dietary fiber intake. Within the vegetable group, beans, peas, and starchy vegetables are the main contributor of total fiber intake (22%). Refined grains provide 9% of total fiber intake (110).

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Dietary Factors

Some of the listed dietary factors (i.e., L-carnitine, coenzyme Q_{10}, and lipoic acid) can be synthesized by the body.

- L-Carnitine
- Coenzyme Q_{10}
- Lipoic Acid
- Phytochemicals
  - Carotenoids
  - Chlorophyll and Chlorophyllin
  - Curcumin
  - Fiber
  - Flavonoids
  - Garlic
  - Indole-3-Carbinol
  - Isothiocyanates
  - Lignans
  - Phytosterols
  - Resveratrol
  - Soy Isoflavones

L-Carnitine

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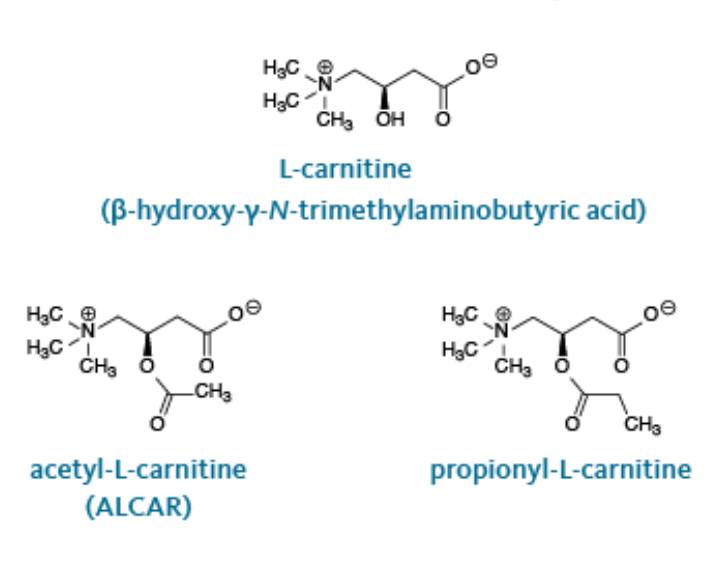
Summary

- Our body produces L-carnitine from the essential amino acid lysine via a specific biosynthetic pathway. Healthy individuals, including strict vegetarians, generally synthesize enough L-carnitine to prevent deficiency. However, certain conditions like pregnancy may result in increased excretion of L-carnitine, potentially increasing the risk for deficiency. *(More information)*
- Because of its role in the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix, L-carnitine is critical for mitochondrial fatty acid β-oxidation. *(More information)*
- L-Carnitine supplementation is indicated for the treatment of primary systemic carnitine deficiency, which is caused by mutations in the gene that codes for the carnitine transporter, OCTN2. *(More information)*
- L-Carnitine is also approved for the treatment of carnitine deficiencies secondary to inherited diseases, such as propionyl-CoA carboxylase deficiency and medium chain acyl-CoA dehydrogenase deficiency, and in patients with end-stage renal disease undergoing hemodialysis. *(More information)*
- Evidence from randomized controlled trials suggests that L-carnitine or acylcarnitine esters may be useful adjuncts to standard medical treatment in individuals with cardiovascular disease. *(More information)*
- Routine administration of L-carnitine to people with end-stage renal disease undergoing hemodialysis is not recommended unless it is to treat carnitine deficiency. *(More information)*
- Acetyl-L-carnitine (ALCAR) may help reduce the severity of chemotherapy-induced peripheral neuropathy. High-quality evidence is needed to evaluate whether ALCAR may benefit the treatment of peripheral neuropathies associated with diabetes or caused by antiretroviral therapy. *(More information)*
- There is some low-quality evidence to suggest that supplemental L-carnitine or ALCAR may be beneficial as adjuncts to standard medical therapy of depression, Alzheimer's disease, and hepatic encephalopathy. *(More information)*
- There is little evidence that L-carnitine supplementation improves cancer-related fatigue, low fertility, or overall physical health. *(More information)*
- If you choose to take L-carnitine supplements, the Linus Pauling Institute recommends acetyl-L-carnitine at a daily dose of 0.5 to 1 g. Note that supplemental L-carnitine (doses, 0.6-7.0 g) is less efficiently absorbed compared to smaller amounts in food. *(More information)*

Introduction

L-Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is a derivative of the amino acid, lysine (**Figure 1**). It was first isolated from meat (*carnus* in Latin) in 1905. Only the L-isomer of carnitine is biologically active (1). L-Carnitine appeared to act as a vitamin in the mealworm (*Tenebrio molitor*) and was therefore termed vitamin B_T (2). Vitamin B_T, however, is a misnomer because humans and other higher organisms can synthesize L-carnitine (see Metabolism and Bioavailability). Under certain conditions, the demand for L-carnitine may exceed an individual's capacity to synthesize it, making it a conditionally essential nutrient (3, 4).

Figure 1. Chemical Structures of L-Carnitine and Two Acylcarnitine Derivatives



[Figure 1 - Click to Enlarge]

Metabolism and Bioavailability

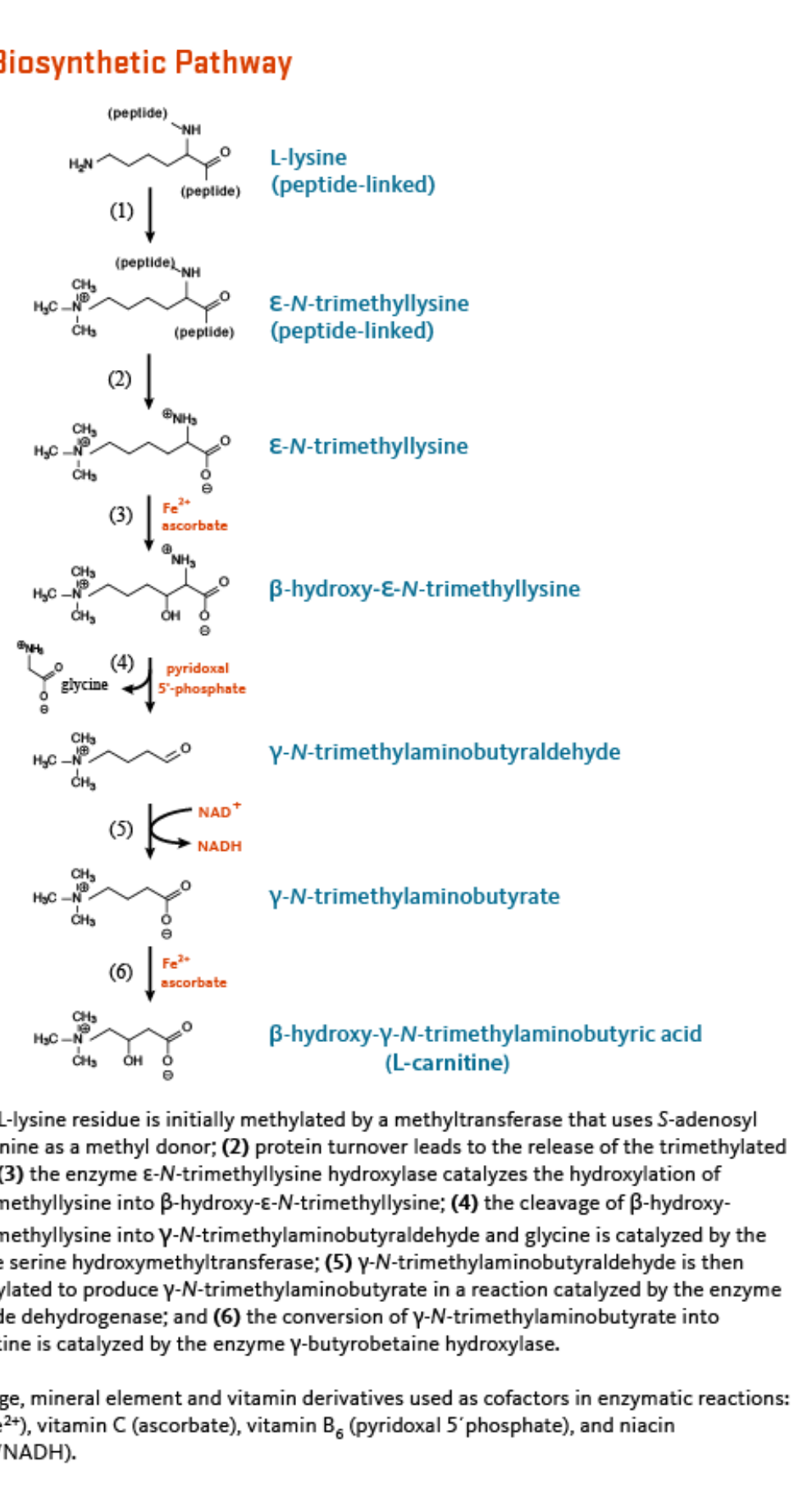
In healthy people, carnitine homeostasis is maintained through endogenous biosynthesis of L-carnitine, absorption of carnitine from dietary sources, and reabsorption of carnitine by the kidneys (5).

Endogenous biosynthesis

Humans can synthesize L-carnitine from the amino acids lysine and methionine in a multi-step process occurring across several cell compartments (cytosol, lysosomes, and mitochondria) (reviewed in 6). Across different organs, protein-bound lysine is methylated to form ε-N-trimethyllysine in a reaction catalyzed by specific lysine methyltransferases that use S-adenosyl-methionine (derived from methionine) as a methyl donor. ε-N-Trimethyllysine is released for carnitine synthesis by protein hydrolysis. Four enzymes are involved in endogenous L-carnitine biosynthesis (**Figure 2**). They are all ubiquitous except γ-butyrobetaine hydroxylase is absent from cardiac and skeletal muscle. This enzyme is, however, highly expressed in human liver, testes, and kidney (7).

L-carnitine is primarily synthesized in the liver and transported via the bloodstream to cardiac and skeletal muscle, which rely on L-carnitine for fatty acid oxidation yet cannot synthesize it (8). The rate of L-carnitine biosynthesis in humans was studied in strict vegetarians (i.e., in people who consume very little dietary carnitine) and estimated to be 1.2 µmol/kg of body weight/day (9). The rate of L-carnitine synthesis depends on the extent to which peptide-linked lysines are methylated and the rate of protein turnover. There is some indirect evidence to suggest that excess lysine in the diet may increase endogenous L-carnitine synthesis; however, changes in dietary carnitine intake level or in renal reabsorption do not appear to affect the rate of endogenous L-carnitine synthesis (6).

Figure 2. Carnitine Biosynthetic Pathway



(1) An L-lysine residue is initially methylated by a methyltransferase that uses *S*-adenosyl methionine as a methyl donor; **(2)** protein turnover leads to the release of the trimethylated lysine; **(3)** the enzyme ε-*N*-trimethyllysine hydroxylase catalyzes the hydroxylation of ε-*N*-trimethyllysine into β-hydroxy-ε-*N*-trimethyllysine; **(4)** the cleavage of β-hydroxy-ε-*N*-trimethyllysine into γ-*N*-trimethylaminobutyraldehyde and glycine is catalyzed by the enzyme serine hydroxymethyltransferase; **(5)** γ-*N*-trimethylaminobutyraldehyde is then hydroxylated to produce γ-*N*-trimethylaminobutyrate in a reaction catalyzed by the enzyme aldehyde dehydrogenase; and **(6)** the conversion of γ-*N*-trimethylaminobutyrate into L-carnitine is catalyzed by the enzyme γ-butyrobetaine hydroxylase.

In orange, mineral element and vitamin derivatives used as cofactors in enzymatic reactions: iron (Fe^{2+}), vitamin C (ascorbate), vitamin B_6 (pyridoxal 5'phosphate), and niacin (NAD^+/NADH).

[Figure 2 - Click to Enlarge]

Absorption of exogenous L-carnitine

Dietary L-carnitine

The bioavailability of L-carnitine from food can vary depending on dietary composition. For instance, one study reported that bioavailability of L-carnitine in individuals adapted to low-carnitine diets (i.e., vegetarians) was higher (66%-86%) than in those adapted to high-carnitine diets (i.e., regular red meat eaters; 54%-72%) (10). The remainder is degraded by colonic bacteria.

L-carnitine supplements

While bioavailability of L-carnitine from the diet is quite high (see Dietary L-carnitine), absorption from oral L-carnitine supplements is considerably lower. The bioavailability of L-carnitine from oral supplements (doses, 0.6 to 7 g) ranges between 5% and 25% of the total dose (5). Less is known regarding the metabolism of the acetylated form of L-carnitine, acetyl-L-carnitine (ALCAR); however, the bioavailability of ALCAR is thought to be higher than that of L-carnitine. The results of *in vitro* experiments suggested that ALCAR might be partially hydrolyzed upon intestinal absorption (11). In humans, administration of 2 g/day of ALCAR for 50 days increased plasma ALCAR concentrations by 43%, suggesting that either ALCAR was absorbed without prior hydrolysis or that L-carnitine was re-acetylated in the enterocytes (5).

Elimination and reabsorption

L-Carnitine and short-chain acylcarnitine derivatives (esters of L-carnitine; see Figure 1) are excreted by the kidneys. Renal reabsorption of free L-carnitine is normally very efficient; in fact, an estimated 95% is thought to be reabsorbed by the kidneys (1). Therefore, carnitine excretion by the kidney is usually very low. However, several conditions can decrease the efficiency of carnitine reabsorption and, correspondingly, increase carnitine excretion. Such conditions include high-fat, low-carbohydrate diets; high-protein diets; pregnancy; and certain disease states (see Primary systemic carnitine deficiency) (12). In addition, when circulating L-carnitine concentration increases, as in the case of oral supplementation, renal reabsorption of L-carnitine may become saturated, resulting in increased urinary excretion of L-carnitine (5). Dietary or supplemental L-carnitine that is not absorbed by enterocytes is degraded by colonic bacteria to form two principal products, trimethylamine and γ-butyrobetaine. γ-Butyrobetaine is eliminated in the feces; trimethylamine is efficiently absorbed and metabolized to trimethylamine-N-oxide, which is excreted in the urine (13).

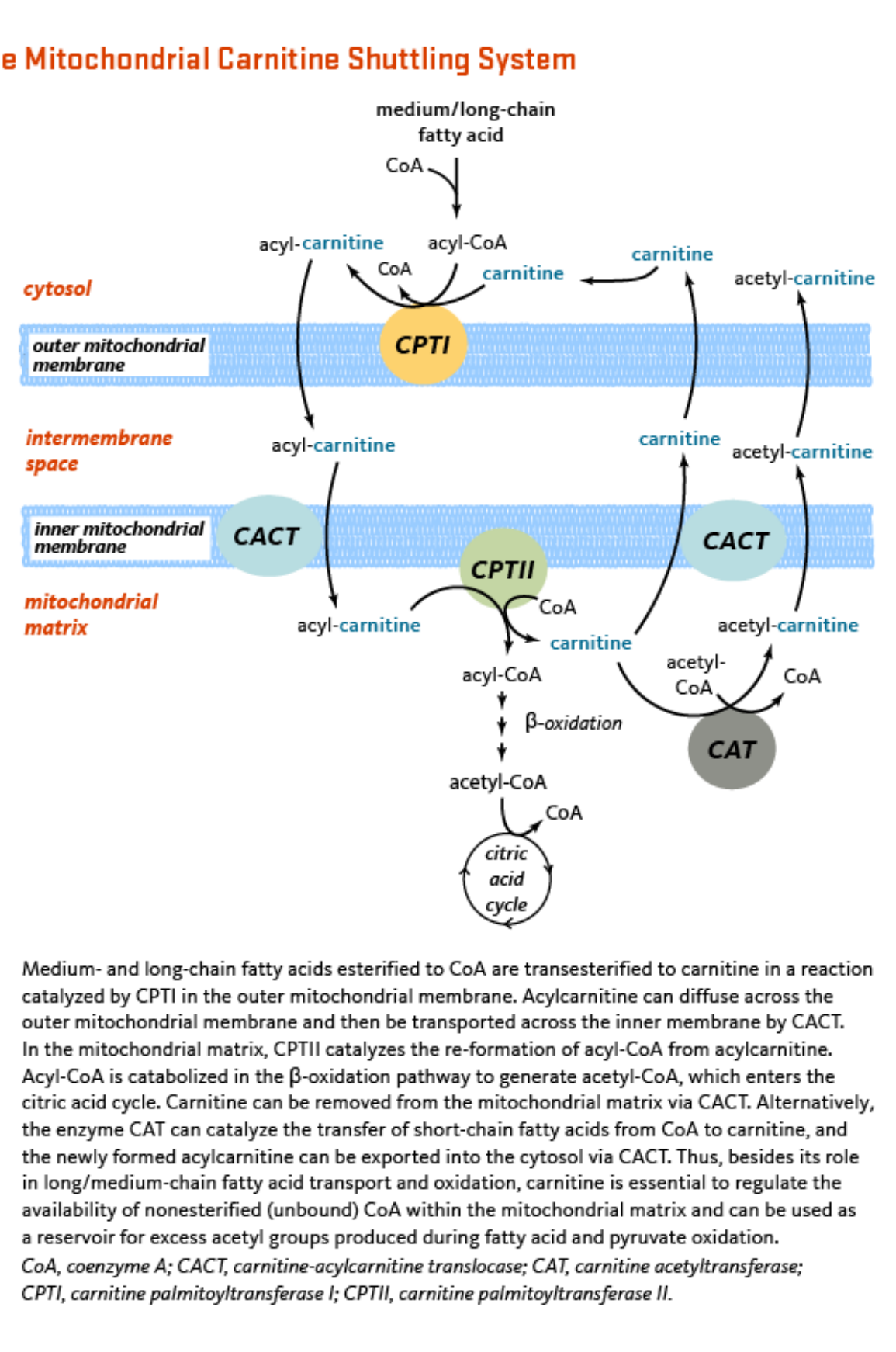
Biological Activities

Mitochondrial oxidation of long-chain fatty acids

L-Carnitine is synthesized primarily in the liver but also in the kidneys and then transported to other tissues. It is most concentrated in tissues that use fatty acids as their primary fuel, such as skeletal and cardiac muscle. In this regard, L-carnitine plays an important role in energy production by conjugating to fatty acids for transport from the cytosol into the mitochondria (6).

L-Carnitine is required for mitochondrial β-oxidation of long-chain fatty acids for energy production (1). Long-chain fatty acids must be esterified to L-carnitine (acylcarnitine) in order to enter the mitochondrial matrix where β-oxidation occurs (**Figure 3**). On the outer mitochondrial membrane, CPTI (carnitine-palmitoyl transferase I) catalyzes the transfer of medium/long-chain fatty acids esterified to coenzyme A (CoA) to L-carnitine. This reaction is a rate-controlling step for the β-oxidation of fatty acid (13). A transport protein called CACT (carnitine-acylcarnitine translocase) facilitates the transport of acylcarnitine across the inner mitochondrial membrane. On the inner mitochondrial membrane, CPTII (carnitine-palmitoyl transferase II) catalyzes the transfer of fatty acids from L-carnitine to free CoA. Fatty acyl-CoA is then metabolized through β-oxidation in the mitochondrial matrix, ultimately yielding propionyl-CoA and acetyl-CoA (6). Carnitine is eventually recycled back to the cytosol (**Figure 3**).

Figure 3. The Mitochondrial Carnitine Shuttling System



Medium- and long-chain fatty acids esterified to CoA are transesterified to carnitine in a reaction catalyzed by CPTI in the outer mitochondrial membrane. Acylcarnitine can diffuse across the outer mitochondrial membrane and then be transported across the inner membrane by CACT. In the mitochondrial matrix, CPTII catalyzes the re-formation of acyl-CoA from acylcarnitine. Acyl-CoA is catabolized in the β-oxidation pathway to generate acetyl-CoA, which enters the citric acid cycle. Carnitine can be removed from the mitochondrial matrix via CACT. Alternatively, the enzyme CAT can catalyze the transfer of short-chain fatty acids from CoA to carnitine, and the newly formed acylcarnitine can be exported into the cytosol via CACT. Thus, besides its role in long/medium-chain fatty acid transport and oxidation, carnitine is essential to regulate the availability of nonesterified (unbound) CoA within the mitochondrial matrix and can be used as a reservoir for excess acetyl groups produced during fatty acid and pyruvate oxidation.
CoA, coenzyme A; CACT, carnitine-acylcarnitine translocase; CAT, carnitine acetyltransferase; CPTI, carnitine palmitoyltransferase I; CPTII, carnitine palmitoyltransferase II.

[Figure 3 - Click to Enlarge]

Regulation of energy metabolism through modulation of acyl CoA:CoA ratio

Free (nonesterified) CoA is required as a cofactor for numerous cellular reactions. The flux through pathways that require nonesterified CoA, such as the oxidation of glucose, may be reduced if all the CoA available in a given cell compartment is esterified. Carnitine can increase the availability of nonesterified CoA for these other metabolic pathways (6). Within the mitochondrial matrix, CAT (carnitine acetyl transferase) catalyzes the transesterification of short- and medium-chain fatty acids from CoA to carnitine (**Figure 3**). The resulting acylcarnitine esters (e.g., acetylcarnitine) can remain in the mitochondrial matrix or be exported back into the cytosol via CACT. Free (nonesterified) CoA can then participate in other reactions, such as the generation of acetyl-CoA from pyruvate in a reaction catalyzed by pyruvate dehydrogenase (14). Acetyl-CoA can then be oxidized to produce energy (ATP) in the citric acid cycle.

Other functions in cellular metabolism

In addition to its importance for energy production, L-carnitine was shown to display direct antioxidant properties *in vitro* (15). Age-related declines in mitochondrial function and increases in mitochondrial oxidant production are thought to be important contributors to the adverse effects of aging. Tissue L-carnitine concentrations have been found to decline with age in humans and animals (16). The expression of most proteins involved in the transport of carnitine (OCTN2) and the acylcarnitine shuttling system across the mitochondrial membrane (CPTIa, CPTII, and CAT; **Figure 3**) was also found to be much lower in the white blood cells of healthy older adults than of younger adults (17).

Preclinical studies in rodents showed that supplementation with high doses of acetyl-L-carnitine (ALCAR; **Figure 1**) reversed a number of age-related changes in liver mitochondrial function yet increased liver mitochondrial oxidant production (18). ALCAR supplementation in rats has also been found to improve or reverse age-related mitochondrial declines in skeletal and cardiac muscular function (19, 20). Co-supplementation of aged rats with L-carnitine and α-lipoic acid blunted age-related increases in reactive oxygen species (ROS), lipid peroxidation, protein carbonylation, and DNA strand breaks in a variety of tissues (heart, skeletal muscle, and brain) (21-30). Co-supplementation for three months improved both the number of total and intact mitochondria and mitochondrial ultrastructure of neurons in the hippocampus (30). Although ALCAR exerts antioxidant activities in rodents, it is not known whether taking high doses of ALCAR will have similar effects in humans.

Deficiency

Nutritional carnitine deficiencies have not been identified in healthy people without metabolic disorders, suggesting that most people can synthesize enough L-carnitine (1). Even strict vegetarians (vegans) show no signs of carnitine deficiency, despite the fact that most dietary carnitine is derived from animal sources (9). Infants, particularly premature infants, are born with low stores of L-carnitine, which could put them at risk of deficiency given their rapid rate of growth. One study reported that infants fed carnitine-free, soy-based formulas grew normally and showed no signs of a clinically relevant carnitine deficiency; however, some biochemical measures related to lipid metabolism differed significantly from infants fed the same formula supplemented with L-carnitine (31). Soy-based infant formulas are now fortified with the amount of L-carnitine normally found in human milk (32).

Carnitine status

Renal filtration maintains plasma concentrations of free carnitine around 40 to 50 micromoles (µmol)/L, while plasma concentrations of acetyl-L-carnitine (ALCAR; the most abundant carnitine ester) are around 3 to 6 µmol/L (8). Regardless of the etiology, plasma concentrations of free carnitine ≤20 µmol/L and increased acylcarnitine/free carnitine ratios (≥0.4) are considered abnormal (6). Low carnitine status is generally due to impaired mitochondrial energy metabolism or to carnitine not being efficiently reabsorbed by the kidneys. The rate of carnitine excretion is not a useful indicator of carnitine status because it can vary with dietary carnitine intake and other physiologic parameters. At present, there is no test that assesses functional carnitine deficiency in humans (6).

Primary systemic carnitine deficiency

Primary systemic carnitine deficiency is a rare, autosomal recessive disorder caused by mutations (including deletions) in the *SLC22A5* gene coding for carnitine transporter protein OCTN2 (organic cation transporter novel 2) (33). Individuals with defective carnitine transport have poor intestinal absorption of dietary L-carnitine, impaired L-carnitine reabsorption by the kidneys (i.e., increased urinary loss of L-carnitine), and defective L-carnitine uptake by muscles (4). The clinical presentation can vary widely depending on the type of mutation affecting *SLC22A5* and the phenotypic manifestation of the mutation, i.e., age of onset, organ involvement, and severity of symptoms at the time of diagnosis (34). The disorder usually presents in early childhood and is characterized by episodes of hypoketotic hypoglycemia (that can cause encephalopathy), hepatomegaly, elevated liver enzymes (transaminases), and hypoammonemia in infants; progressive cardiomyopathy, elevated creatine kinase, and skeletal myopathy in childhood; or fatigability in adulthood (34, 35). The metabolic and myopathic symptoms in infants and children can be fatal such that treatment should start promptly to prevent irreversible organ damage (34). The diagnosis is established by demonstrating abnormally low plasma free carnitine concentrations, reduced carnitine transport of fibroblasts from skin biopsy, and molecular analysis of the gene coding for OCTN2 (33, 34). Treatment consists of pharmacological doses of L-carnitine that are meant to maintain a normal blood carnitine concentration, thereby preventing the risk of hypoglycemia and correcting metabolic and myopathic manifestations (34).

Secondary carnitine deficiency or depletion

Secondary carnitine deficiency or depletion may result from either genetic or acquired conditions.

Hereditary causes include genetic defects in the metabolism of amino acids, cholesterol, and fatty acids, such as propionyl-CoA carboxylase deficiency (aka propionic acidemia) and medium chain acyl-CoA dehydrogenase deficiency (36). Such inherited disorders lead to a buildup of organic acids, which are subsequently removed from the body via urinary excretion of acylcarnitine esters. Increased urinary losses of carnitine can lead to the systemic depletion of carnitine (6).

Systemic carnitine depletion can also occur in disorders of impaired renal reabsorption. For instance, Fanconi's syndrome is a hereditary or acquired condition in which the proximal tubular reabsorption function of the kidneys is impaired (37). This malfunction consequently results in increased urinary losses of carnitine. Patients with renal disease who undergo hemodialysis are at risk for secondary carnitine deficiency because hemodialysis removes carnitine from the blood (see End-stage renal disease) (38).

One example of an exclusively acquired carnitine deficiency involves chronic use of pivalate-conjugated antibiotics. Pivalate is a branched-chain fatty acid anion that is metabolized to form an acyl-CoA ester, which is transesterified to carnitine and subsequently excreted in the urine as pivaloyl carnitine. Urinary losses of carnitine via this route can be 10-fold greater than the sum of daily carnitine intake and biosynthesis and lead to systemic carnitine depletion (see Drug interactions) (39).

Finally, a number of inherited mutations in genes involved in carnitine shuttling and fatty acid oxidation pathways do not systematically result in carnitine depletion (such that carnitine supplementation may not help mitigate the symptoms) but lead to abnormal profiles of acylcarnitine esters in blood (35, 40).

Nutrient interactions

Endogenous biosynthesis of L-carnitine is catalyzed by the concerted action of four different enzymes (see Metabolism and Bioavailability) (**Figure 2**). This process requires two essential amino acids (lysine and methionine), iron (Fe^{2+}), vitamin B_6 in the form of pyridoxal 5'-phosphate, niacin in the form of nicotinamide adenine dinucleotide (NAD), and may also require vitamin C (ascorbate) (4). One of the earliest symptoms of vitamin C deficiency is fatigue, thought to be related to decreased synthesis of L-carnitine (41).

Disease Treatment

In most studies discussed below, it is important to note that treatment with L-carnitine or acyl-L-carnitine esters (i.e., acetyl-L-carnitine [ALCAR], propionyl-L-carnitine; **Figure 1**) was generally used as an adjunct to standard medical therapy, not in place of it. It is also important to consider the fact that the bioavailability of L-carnitine and acylcarnitine derivatives administered orally is low (~10-20%) (see Metabolism and Bioavailability). Intravenous administration is more likely to increase plasma carnitine concentration, yet homeostatic mechanisms tightly control blood concentration through metabolism and renal excretion: Up to 90% of 2 g of L-carnitine administered intravenously is excreted into the urine within 12 to 24 hours. Only a fraction of the dose is thought to enter the endogenous carnitine pool — largely found in skeletal muscle (reviewed in 8).

Type 2 diabetes mellitus

Several small clinical trials have explored whether supplemental L-carnitine could improve glucose tolerance in people with impaired glucose metabolism. A potential benefit of L-carnitine in these patients is based on the fact that it can (i) increase the oxidation of long-chain fatty acids which accumulation may contribute to insulin resistance in skeletal muscle, and (ii) enhance glucose utilization by reducing acyl-CoA concentration within the mitochondrial matrix (see Biological Activities) (42). A meta-analysis of five trials in participants with either impaired fasting glucose, type 2 diabetes mellitus, or nonalcoholic steatohepatitis found evidence of an improvement in insulin resistance with supplemental L-carnitine compared to placebo (43). Another meta-analysis of four randomized, placebo-controlled trials found evidence of a reduction in fasting plasma glucose concentration and no improvement of glycated hemoglobin concentration in subjects with type 2 diabetes mellitus supplemented with acetyl-L-carnitine (ALCAR) (44). A third meta-analysis of 16 trials suggested that supplementation with (acyl)-L-carnitine may reduce fasting blood glucose and glycated hemoglobin concentrations, but not resistance to insulin (45). In a recent double-blind, randomized, placebo-controlled trial, the effect of ALCAR was examined in 229 participants treated for type 2 diabetes mellitus, hypertension, and dyslipidemia (46). ALCAR supplementation (1 g/day for 6 months) had no effect on systolic or diastolic blood pressure, markers of kidney function (i.e., glomerular filtration rate and albuminuria), markers of glucose homeostasis (i.e., glucose disposal rate, glycated hemoglobin concentration, and a measure of insulin resistance), and blood lipid profile (i.e., concentrations of triglycerides, lipoprotein (a), LDL-cholesterol, HDL-cholesterol, and total cholesterol) (46).

Cardiovascular disease

In the studies discussed below it is important to note that treatment with L-carnitine or propionyl-L-carnitine was used as an adjunct (in addition) to appropriate medical therapy, not in place of it.

Myocardial infarction

Myocardial infarction (MI) occurs when an atherosclerotic plaque in a coronary artery ruptures and obstructs the blood supply to the heart muscle, causing injury or damage to the heart (see the page on Heart Attack). Several clinical trials have explored whether L-carnitine administration immediately after MI diagnosis could reduce injury to heart muscle resulting from ischemia and improve clinical outcomes. An early trial in 160 men and women diagnosed with a recent MI showed that oral L-carnitine (4 g/day) in addition to standard pharmacological treatment for one year significantly reduced mortality and the occurrence of angina attacks compared to the control (47). In another controlled trial in 96 patients, treatment with intravenous L-carnitine (5 g bolus followed by 10 g/day for three days) following a MI resulted in lower concentrations of creatine kinase-MB and troponin-I, two markers of cardiac injury (48). However, not all clinical trials have found L-carnitine supplementation to be beneficial after MI. For example, in a randomized, double-blind, placebo-controlled trial in 60 participants diagnosed with an acute MI, neither mortality nor echocardiographic measures of cardiac function differed between patients treated with intravenous L-carnitine (6 g/day) for seven days followed by oral L-carnitine (3 g/day) for three months and those given a placebo (49). Another randomized placebo-controlled trial in 2,330 patients with acute MI, L-carnitine therapy (9 g/day intravenously for five days, then 4 g/day orally for six months) did not affect the risk of heart failure and death six months after MI (50).

A 2013 meta-analysis of randomized controlled trials found that L-carnitine therapy in patients who experienced an MI reduced the risks of all-cause mortality (-27%; 11 trials; 3,579 participants), ventricular arrhythmias (-65%; five trials; 229 participants), and angina attacks (-40%; 2 trials; 261 participants), but had no effect on the risks of having a subsequent myocardial infarction or developing heart failure (51). Because about 90% of oral L-carnitine supplements is unlikely to be absorbed, one could ask whether the efficacy is equivalent between protocols using both intravenous and oral administration and those using oral administration only (8). This has not been examined in subgroup analyses.

Heart failure

Heart failure is described as the heart's inability to pump enough blood for all of the body's needs (see the page on Heart Failure). In coronary heart disease, accumulation of atherosclerotic plaque in the coronary arteries may prevent heart regions from getting adequate circulation, ultimately resulting in cardiac damage and impaired pumping ability. Myocardial infarction may also damage the heart muscle, which could potentially lead to heart failure. Further, the diminished heart's capacity to pump blood in cases of dilated cardiomyopathy may lead to heart failure. Because physical exercise increases the demand on the weakened heart, measures of exercise tolerance are frequently used to monitor the severity of heart failure. Echocardiography is also used to determine the left ventricular ejection fraction (LVEF), an objective measure of the heart's pumping ability. An LVEF of less than 40% is indicative of systolic heart failure (52).

An abnormal acylcarnitine profile and a high acylcarnitine to free carnitine ratio in the blood of patients with heart failure have been linked to disease severity and poor prognosis (53-55). Addition of L-carnitine to standard medical therapy for heart failure has been evaluated in several clinical trials. A 2013 meta-analysis of 17 randomized, placebo-controlled studies in a total of 1,625 participants with heart failure found that oral L-carnitine (1.5-6 g/day for seven days to three years) significantly improved several measures of cardiac functional capacity (including exercise tolerance and markers of the left ventricle function), yet had no impact on all-cause mortality (56).

Angina pectoris

Angina pectoris is chest pain that occurs when the coronary blood supply is insufficient to meet the metabolic needs of the heart muscle (as with ischemic heart disease; see the page on Angina Pectoris) (57). In a prospective cohort study in over 4,000 participants with suspected angina pectoris, elevated concentrations of certain acylcarnitine intermediates in blood were associated with fatal and non-fatal acute myocardial infarction (58). In early studies, the addition of oral L-carnitine or propionyl-L-carnitine to pharmacologic therapy for chronic stable angina modestly improved exercise tolerance and decreased electrocardiographic signs of ischemia during exercise testing in some angina patients (59-61). Another early study examined hemodynamic and angiographic variables before, during, and after administering intravenous propionyl-L-carnitine (15 mg/kg body weight) in men with myocardial dysfunction and angina pectoris (62). In this study, propionyl-L-carnitine decreased myocardial ischemia, evidenced by significant reductions in ST-segment depression and left ventricular end-diastolic pressure (62). No recent and/or large-scale studies have been conducted to further examine the potential benefit of L-carnitine or propionyl-L-carnitine in the management of angina pectoris.

Intermittent claudication in peripheral arterial disease

In peripheral arterial disease, atherosclerosis of the arteries that supply the lower extremities may diminish blood flow to the point that the metabolic needs of exercising muscles are not sufficiently met, thereby leading to ischemic leg or hip pain known as claudication (see the page on Intermittent Claudication in Peripheral Arterial Disease) (63). Several clinical trials have found that treatment with propionyl-L-carnitine improves exercise tolerance in some patients with intermittent claudication. In a double-blind, placebo-controlled, dose-titration study, 1 to 3 g/day of oral propionyl-L-carnitine for 24 weeks was well tolerated and improved maximal walking distance in patients with intermittent claudication (64). In a randomized, placebo-controlled study of 495 patients with intermittent claudication, 2 g/day of propionyl-L-carnitine for 12 months significantly increased maximal walking distance and the distance walked prior to the onset of claudication in patients whose initial maximal walking distance was less than 250 meters (m), but no effect was seen in patients who had an initial maximal walking distance greater than 250 m (65). More recent trials have associated oral propionyl-L-carnitine supplementation (2 g/day for several months) with improved walking distance and claudication onset time (66, 67), as well as with higher pain-free walking distance and higher ankle-brachial index (a diagnostic measure of peripheral arterial disease) (68). Two 2013 systematic reviews of interventions concluded that the modest benefit of propionyl-L-carnitine on walking performance was equivalent or superior to that obtained with drugs approved for claudication in the US (e.g., pentoxyphylline, cilostazol) yet inferior to improvements seen with supervised exercise interventions (69, 70).

End-stage renal disease

L-Carnitine and short/medium-chain acylcarnitine molecules are removed from the circulation during hemodialysis. Both L-carnitine loss into the dialysate and impaired synthesis by the kidneys contribute to a progressive carnitine deficiency in patients with end-stage renal disease (ESRD) undergoing hemodialysis (71). The low clearance of long-chain acylcarnitine molecules leads to a high acylcarnitine-to-L-carnitine ratio that has been associated with a higher risk of cardiovascular mortality (72). Carnitine depletion in patients undergoing hemodialysis may lead to various conditions, such as muscle weakness and fatigue, plasma lipid abnormalities, and refractory anemia. A 2014 systematic review and meta-analysis of 31 randomized controlled trials in a total of 1,734 patients with ESRD found that L-carnitine treatment — administered either orally or intravenously — resulted in reductions of serum C-reactive protein (a marker of inflammation and predictor of mortality in patients undergoing hemodialysis) and LDL-cholesterol, although the latter was not deemed to be clinically relevant (73). There was no effect of L-carnitine on other serum lipids (i.e., total and HDL-cholesterol, triglycerides) and anemia-related indicators (i.e., hemoglobin concentration, hematocrit, albumin, and required dose of recombinant erythropoietin) (73).

The US National Kidney Foundation did not recommend routine administration of L-carnitine to subjects undergoing dialysis yet encouraged the development of trials in patients with select symptoms that do not respond to standard therapy, i.e., persistent muscle cramps or hypotension during dialysis, severe fatigue, skeletal muscle weakness or myopathy, cardiomyopathy, and anemia requiring large doses of erythropoietin (74, 75).

Finally, the use of L-carnitine (10-20 mg/kg body weight given as a slow bolus injection) is approved by the US FDA to treat L-carnitine deficiency in subjects with ESRD undergoing hemodialysis (76).

Peripheral neuropathy

Antiretroviral-related peripheral neuropathy

The use of certain antiretroviral agents (nucleoside analogs) has been associated with an increased risk of developing peripheral neuropathy in HIV-positive individuals (77, 78). Small, uncontrolled, open-label intervention studies have suggested a beneficial effect of acetyl-L-carnitine (ALCAR) in patients with painful neuropathies. An early uncontrolled study found that 10 out of 16 HIV-positive subjects with painful neuropathy reported improvement after three weeks of intravenous or intramuscular ALCAR treatment (79). Results from another uncontrolled intervention in 21 HIV-positive patients suggested that long-term (two to four years) oral ALCAR supplementation (1.5 g/day) may be a beneficial adjunct to antiretroviral therapy to improve neuropathic symptoms in some HIV-infected individuals (80, 81). Additionally, two small studies in participants presenting with antiretroviral-induced neuropathy found significant reduction in subjects' mean pain intensity with oral ALCAR (1-3 g/day) for 4 to 24 weeks, but no effect on objective neurophysiological parameters was found (82, 83).

A double-blind, placebo-controlled trial in 90 HIV-positive patients with symptomatic distal symmetrical polyneuropathy found no benefit of intramuscular injection with 1 g/day of ALCAR for two weeks in the intention-to-treat analysis, but there was some pain relief in the group of 66 patients who completed the trial (84). Large-scale, controlled studies are needed before any conclusions can be drawn.

Diabetic peripheral neuropathy

Peripheral nerve dysfunction occurs in about 50% of people with diabetes mellitus, and chronic neuropathic pain is present in about one-third of people with diabetic peripheral neuropathy (85). Advanced stages of diabetic peripheral neuropathy can lead to recurrent foot ulcers and infections, and eventually amputations (86). A 2019 systematic review (87) identified three placebo-controlled interventions that examined the effect of oral supplementation with acetyl-L-carnitine (ALCAR; 1.5-3.0 g/day for one year) in individuals with diabetic peripheral neuropathy (3, 88). Low-quality evidence suggested a lower level of pain with ALCAR, as measured with a visual scale analog. Low-quality evidence from another trial that compared the effect of ALCAR (1.5 g/day) with that of methylcobalamin (1.5 mg/day) for 24 weeks suggested no difference between treatments regarding the extent of functional disability (using the Neuropathy Disability Scale) or measures of symptom quality and severity (using the Neuropathy Symptom Scale) (89).

Chemotherapy-induced peripheral neuropathy

A few randomized, double-blind, placebo-controlled trials have examined whether ALCAR might help prevent or treat chemotherapy-induced peripheral neuropathy. A trial in 150 participants with either ovarian cancer or castration-resistant prostate cancer found no evidence that ALCAR (1g every 3 days) given with the anticancer drug sagopilone (for up to six cycles of treatment) reduced the overall risk of peripheral neuropathy compared to a placebo (90). However, ALCAR reduced the risk of high-grade sagopilone-induced neuropathy (90). In contrast, another trial in 409 women with breast cancer found that ALCAR (3 g/day for 24 weeks) increased anticancer drug (taxanes)-induced peripheral neuropathy and decreased measures of functional status compared to placebo (91). A follow-up study reported that the negative impact of 24-week treatment with ALCAR was still observed at week 52; however, no differences between ALCAR and placebo were apparent at week 104 (92). Finally, one trial in 239 participants already suffering from chemotherapy-induced peripheral neuropathy reported a reduction in the severity of neuropathic symptoms with ALCAR (3 g/day for eight weeks) compared to placebo (93). Improvements in electrophysiological parameters were also observed with ALCAR treatment (93).

The results from these trials are conflicting and thus difficult to interpret. The efficacy of ALCAR in the prevention and treatment of chemotherapy-induced peripheral neuropathy remains to be established (94).

Depression

A 2018 meta-analysis identified 12 randomized controlled trials, including 791 participants, that examined the effect of ALCAR on symptoms of depression (95). Evidence from nine trials suggested a reduction in depressive symptoms with ALCAR (3 g/day for a median 8 weeks) compared to a placebo. Three trials that compared ALCAR treatment (1-3 g/day for 7-12 weeks) and antidepressant medications found ALCAR was as effective as antidepressants in treating depressive symptoms (95). Another meta-analysis of trials that compared the safety profile of antidepressants found evidence of fewer adverse effects, and consequently, better adherence to treatment with ALCAR compared to placebo and in contrast to classical pharmaceutical agents (96).

Alzheimer's disease

The metabolomic profiling of acylcarnitine molecules showed variations in serum concentrations of subjects along the continuum from cognitively healthy to affected by Alzheimer's disease (97). Changes in the blood concentrations of specific acylcarnitines in subjects with either subjective memory complaints, mild cognitive impairment, or Alzheimer's disease, compared to cognitively healthy peers may reflect changes in the transport of fatty acids into the mitochondria and/or impairments in energy production. Several clinical trials conducted in the 1990s examined the effect of acetyl-L-carnitine (ALCAR) treatment on the cognitive performance of patients clinically diagnosed with Alzheimer's disease. Early, small trials suggested a beneficial effect of ALCAR with respect to cognitive decline (98-100), whereas later, larger trials found little-to-no effect compared to placebo (101-103). However, a 2003 systematic review highlighted differences in methodologies between early and later studies that make it difficult to compare results (104). Nevertheless, the pooled analysis of 16 trials suggested improvements in the summary measure of patients' global functioning (assessed with the Clinical Global Impressions [CGI-I] scale) after 12 and 24 weeks of (but not after 52 weeks) of ALCAR treatment (1-3 g/day) and in cognitive performance (assessed with the Mini-Mental State Examination [MMSE] scale) after 24 weeks (but not at 12 or 52 weeks) (104). A 2003 meta-analysis of 21 trials found that ALCAR was superior to placebo in several psychometric tests assessing global patient functioning, attention, memory, and some intellectual functions (105).

Hepatic encephalopathy

Hepatic encephalopathy refers to the occurrence of a spectrum of neuropsychiatric signs or symptoms in individuals with acute or chronic liver disease (106). Subclinical hepatic encephalopathy may not feature any symptoms beyond abnormal behavior on psychometric tests or symptoms that are nonspecific in nature. In contract, overt hepatic encephalopathy can present with disorientation, obvious personality change, inappropriate behavior, somnolence, stupor, confusion, and coma (106). Changes in mental status are thought to be caused by the liver failing to detoxify neurotoxic compounds like ammonia. A 2019 systematic review of five placebo-controlled trials conducted by one group of investigators examined the effect of acetyl-L-carnitine (ALCAR) in 398 participants with cirrhosis and portal hypertension (high blood pressure in the portal vein) and presenting with either subclinical or overt hepatic encephalopathy. ALCAR was either administered orally (4 g/day for 90 days) in four trials or intravenously (4 g/day for three days) in one trial. ALCAR was found to significantly reduce blood ammonium concentration compared to placebo. However, none of the trials reported on serious adverse outcomes, including mortality. Additionally, the evidence was too limited to assess the impact on quality of life or mental and physical fatigue.

Cancer-related fatigue

Fatigue is not uncommon in people who have undergone chemotherapy and survived cancer, with fatigue symptoms depending on the specific type of cancer and treatment. Cancer-related fatigue can persist well beyond the end of chemotherapy and be associated with cognitive and functional decline, insomnia, depression, and a reduction in the quality of life (107). A 2017 systematic review and meta-analysis identified 12 intervention studies that assessed the effect of L-carnitine or ALCAR on cancer-related fatigue (reported as a primary or secondary outcome) in cancer survivors (108). Three studies had no control arm, eight studies were open-label, and eight studies included fewer than 100 participants. Overall, only three studies were deemed of good quality. The meta-analysis of these three randomized, double-blind, placebo-controlled trials found no effect of L-carnitine (0.25-4 g/day for 1 week to 3 months) or ALCAR (3 g/day for 6 months) on the level of cancer-related fatigue (108).

Infertility

L-Carnitine is concentrated in the epididymis, where sperm mature and acquire their motility (109). An early cross-sectional study of 101 fertile and infertile men found that L-carnitine concentrations in semen were positively correlated with the number of sperm, the percentage of motile sperm, and the percentage of normal appearing sperm in the sample (110), suggesting that L-carnitine may play an important role in male fertility. One placebo-controlled, double-blind, cross-over trial in 86 subjects with fertility issues found that supplementation with L-carnitine (2 g/day) for two months improved sperm quality, as evidenced by increases in sperm concentration and motility (111). In another placebo-controlled trial conducted by the same group, similar improvements in sperm motility were observed in participants supplemented with 2g/day of L-carnitine and 1 g/day of acetyl-L-carnitine (ALCAR) for six months (112). In both trials, the effect of carnitine was greater in the most severe cases of asthenozoospermia (reduced sperm motility) at baseline (111, 112). Another placebo-controlled, double-blind, randomized study in 44 men with idiopathic asthenozoospermia found an increase in sperm motility in those given ALCAR alone (3 g/day) or ALCAR (1 g/day) plus L-carnitine (2 g/day) compared to those given L-carnitine alone (2 g/day) or a placebo (113). However, a pooled analysis of the two trials that employed ALCAR found no significant effect of ALCAR and L-carnitine on sperm concentration, motility, and morphology (114). Evidence from larger scale clinical trials is still needed to determine whether L-carnitine and ALCAR could play a role in the treatment of male infertility.

Physical health

Frailty

Frailty is a syndrome prevalent among geriatric populations and characterized by a functional decline and a loss of independence to perform the activities of daily living. Frailty in individuals may include at least three of the following symptoms: unintentional weight loss, exhaustion (poor endurance), weakness (low grip strength), slowness, and physical inactivity (115). It is believed that early stages of frailty are amenable to interventions that could avert adverse outcomes, including the increased risk of hospitalization and premature death (116). The suggestion that carnitine deficiency may lead to frailty through mitochondrial dysfunction (117) has been examined in one trial. This randomized, double-blind, placebo-controlled trial in 58 older adults identified as "pre-frail" found an decrease in a Frailty Index score and an improvement in the hand grip test in individuals supplemented with L-carnitine (1.5 g/day) over 10 weeks but not in those given a placebo (118). However, there was no difference in Frailty Index and hand grip test scores between supplemental L-carnitine and placebo groups.

Skeletal muscle wasting

Loss of skeletal muscle mass is associated with a decrease in muscle strength and occurs with aging (119), as well as in several pathological conditions (120-122). Based on preclinical studies, it has been suggested that L-carnitine supplementation could limit the imbalance between protein anabolism (synthesis) and catabolism (degradation) that leads to skeletal muscle wasting (42). A randomized, double-blind, placebo-controlled trial in 28 older women (ages, 65-70 years) found no effect of L-carnitine supplementation (1.5 g/day for 24 weeks) on serum pro-inflammatory cytokine concentrations, body mass and composition (lean [fat-free] mass and skeletal muscle mass), or measures of skeletal muscle strength (123). In contrast, a retrospective cohort study in patients with cirrhosis found a reduced rate of skeletal muscle loss over at least six months in those who were administered L-carnitine (N=35; mean dose, 1.02 g/day) compared to those who were not (124). Of note, supplementation with L-carnitine was given in patients with cirrhosis to control hyperammonemia (N=27), to reduce muscle cramps (N=6), or to prevent carnitine deficiency (N=2). One major limitation of this study beyond its retrospective design is that patients who received L-carnitine had a significantly different clinical presentation; in particular, liver dysfunction was significantly more severe in these patients than in those who were not supplemented (124).

Muscle cramps

Muscle cramps are involuntary and painful contractions of skeletal muscles. Two uncontrolled studies conducted in participants with cirrhosis found that L-carnitine supplementation was safe to use at doses of 0.9 to 1.2 g/day for eight weeks (125) and 1 g/day for 24 weeks (126) and might be considered to control the frequency of cramps. However, whether supplemental L-carnitine can be efficacious to limit the incidence of muscle cramps in patients with cirrhosis remains unknown. An open-label, non-randomized trial in 69 patients with either type 1 or type 2 diabetes mellitus found a reduction in the incidence of muscle cramps and an improvement in the quality of life of those prescribed 0.6 g/day of L-carnitine for four months compared to controls (127). In contrast, there is little evidence to date to suggest that supplemental L-carnitine could reduce muscle cramps in patients undergoing hemodialysis (128). Well-designed trials are necessary to examine whether L-carnitine could be helpful in the management of cramps.

Physical performance

Interest in the potential of L-carnitine supplementation to improve athletic performance is related to its important roles in energy metabolism. A number of small, poorly controlled studies have reported that either acute (dose given one hour before exercise bout) or short-term (two to three weeks) supplementation with L-carnitine (2 to 4 g/day) supported energy production, cardiorespiratory fitness, and endurance capacity during physical exercise (reviewed in 129). However, in a double-blind, placebo-controlled trial in 32 healthy adults, propionyl-L-carnitine (1 g/day or 3 g/day) for eight weeks did not improve aerobic or anaerobic exercise performance (130). An intervention study compared the effect of L-carnitine supplementation (2 g/day for 12 weeks) on plasma and skeletal muscle carnitine concentrations and physical performance between 16 vegetarian and 8 omnivorous male participants (131). At baseline, plasma carnitine concentration was about 10% lower in vegetarian compared to omnivorous participants. However, the content carnitine in skeletal muscle, phosphocreatine, ATP, glycogen, and lactate, as well as measures of physical performance during exercise were equivalent between vegetarians and omnivores. While L-carnitine supplementation normalized plasma carnitine concentration in vegetarians to that observed in omnivores, there was no effect on energy metabolism and physical performance compared to no supplementation and between vegetarians and omnivores (131).

Sources

Biosynthesis

The normal rate of L-carnitine biosynthesis in humans ranges from 0.16 to 0.48 mg/kg of body weight/day (4). Thus, a 70 kg (154 1b) person would synthesize between 11 and 34 mg of carnitine per day. This rate of synthesis, combined with efficient (95%) L-carnitine reabsorption by the kidneys, is sufficient to prevent deficiency in generally healthy people, including strict vegetarians (132).

Food sources

Meat, poultry, fish, and dairy products are the richest sources of L-carnitine, while fruit, vegetables, and grains contain relatively little L-carnitine. Omnivorous diets have been found to provide 23 to 135 mg/day of L-carnitine for an average 70 kg person, while strict vegetarian diets may provide as little as 1 mg/day for a 70 kg person (8). Between 54% and 86% of L-carnitine from food is absorbed, compared to 5%-25% from oral supplements (0.6-7 g/day) (13). Non-milk-based infant formulas (e.g., soy formulas) should be fortified so that they contain 11 mg/L of L-carnitine. Some carnitine-rich foods and their carnitine content in milligrams (mg) are listed in **Table 1**.

Table 1. L-Carnitine Content of Selected Foods

Food	Serving	L-Carnitine (mg)
Beef steak	3 ounces*	81
Ground beef	3 ounces	80
Pork	3 ounces	24
Canadian bacon	3 ounces	20
Milk (whole)	8 fluid ounces (1 cup)	8
Fish (cod)	3 ounces	5
Chicken breast	3 ounces	3
Ice cream	4 ounces (½ cup)	3
Avocado	1 medium	2
American cheese	1 ounce	1
Whole-wheat bread	2 slices	0.2
Asparagus	6 spears (½ cup)	0.2
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

Intravenous L-carnitine

Intravenous L-carnitine is available by prescription only for the treatment of primary and secondary L-carnitine deficiencies (76).

Oral L-carnitine

Oral L-carnitine is available by prescription for the treatment of primary and secondary L-carnitine deficiencies (76). It is also available without a prescription as a nutritional supplement; supplemental doses usually range from 0.5 to 2 g/day.

Acetyl-L-carnitine

Acetyl-L-carnitine (ALCAR) is available without a prescription as a nutritional supplement. In addition to providing L-carnitine, it provides acetyl groups that may be used in the formation of the neurotransmitter, acetylcholine. Supplemental doses usually range from 0.5 to 2 g/day (133).

Propionyl-L-carnitine

Propionyl-L-carnitine is not approved by the US FDA for use as a drug to prevent or treat any condition. It is, however, available without prescription as a nutritional supplement.

See Figure 1 for the chemical structures of L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine.

Safety

Adverse effects

In general, L-carnitine appears to be well tolerated; no toxic effects have been reported in relation to intakes of high doses of L-carnitine. L-Carnitine supplementation may cause mild gastrointestinal symptoms, including nausea, vomiting, abdominal cramps, and diarrhea. Supplements providing more than 3 g/day may cause a "fishy" body odor. Acetyl-L-carnitine (ALCAR) has been reported to increase agitation in some Alzheimer's disease patients (133). Despite claims that L-carnitine or ALCAR might increase seizures in some individuals with seizure disorders (133), these are not supported by any scientific evidence (134). Only the L-isomer of carnitine is biologically active; the D-isomer may actually compete with L-carnitine for absorption and transport, thereby increasing the risk of L-carnitine deficiency (4). Supplements containing a mixture of the D- and L-isomers (D,L-carnitine) have been associated with muscle weakness in patients with kidney disease. Long-term studies examining the safety of ALCAR supplementation in pregnant and breast-feeding women are lacking (133).

Drug interactions

Pivalic acid combines with L-carnitine and is excreted in the urine as pivaloylcarnitine, thereby increasing L-carnitine losses (see also Secondary carnitine deficiency). Consequently, prolonged use of pivalic acid-containing antibiotics, including pivampicillin, pivmecillinam, pivcephalexin, and cefditoren pivoxil (Spectracef), can lead to secondary L-carnitine deficiency (135). The anticonvulsant valproic acid (Depakene) interferes with L-carnitine biosynthesis in the liver and forms with L-carnitine a valproylcarnitine ester that is excreted in the urine. However, L-carnitine supplements are necessary only in a subset of patients taking valproic acid. Risk factors for L-carnitine deficiency with valproic acid include young age (<2 years), severe neurological problems, use of multiple antiepileptic drugs, poor nutrition, and consumption of a ketogenic diet (135). There is insufficient evidence to suggest that nucleoside analogs used in the treatment of HIV infection (i.e., zidovudine [AZT], didanosine [ddI], zalcitabine [ddC], and stavudine [d4T] or certain cancer chemotherapy agents (i.e., ifosfamide, cisplatin) increase the risk of secondary L-carnitine deficiency (135).

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Coenzyme Q10

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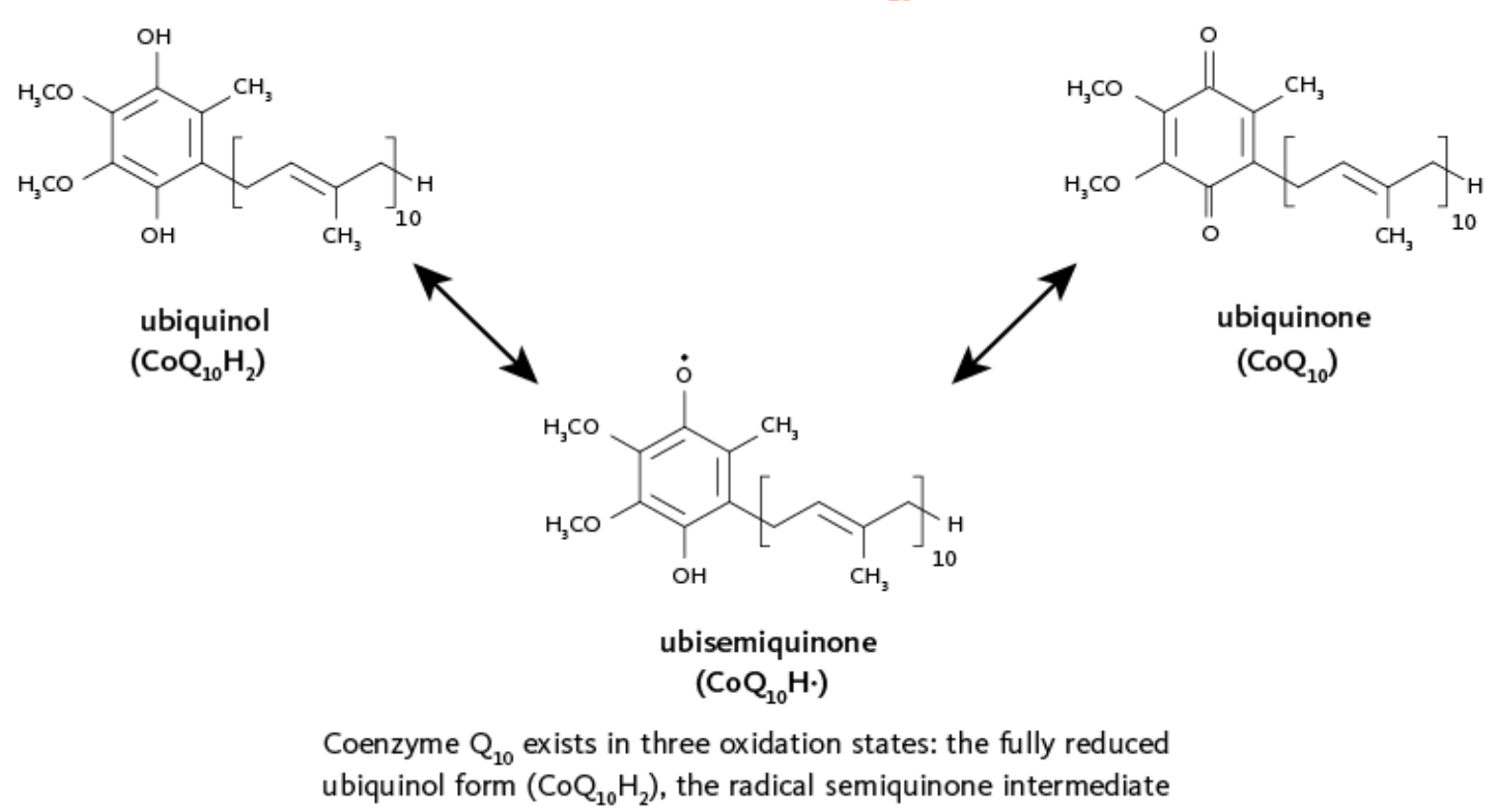
Summary

- Coenzyme Q$_{10}$ is a fat-soluble compound that is synthesized by the body and can be obtained from the diet. *(More information)*
- Coenzyme Q$_{10}$ plays a central role in mitochondrial oxidative phosphorylation and the production of adenosine triphosphate (ATP). It also functions as an antioxidant in cell membranes and lipoproteins. *(More information)*
- Endogenous synthesis and dietary intake provide sufficient coenzyme Q$_{10}$ to prevent deficiency in healthy people, although coenzyme Q$_{10}$ concentrations in tissues decline with age. *(More information)*
- Oral supplementation of coenzyme Q$_{10}$ increases coenzyme Q$_{10}$ concentrations in plasma and lipoproteins, but it is unclear whether concentrations in peripheral tissues are increased, especially in healthy individuals. *(More information)*
- Oral high-dose coenzyme Q$_{10}$ is usually effective to treat mitochondrial disorders that are caused by mutations in coenzyme Q$_{10}$ biosynthetic genes. *(More information)*
- There is some evidence to suggest that coenzyme Q$_{10}$ supplementation may be a useful adjunct to conventional medical therapy for congestive heart failure and in patients undergoing coronary artery bypass graft surgery. *(More information)*
- There are currently no proven therapeutic benefits of coenzyme Q$_{10}$ supplementation in diabetes mellitus, neurodegenerative diseases, inherited ataxias, or breast cancer. *(More information)*
- Coenzyme Q$_{10}$ supplementation does not appear to improve athletic performance. *(More information)*
- Although coenzyme Q$_{10}$ supplements are relatively safe, they may decrease the anticoagulant efficacy of warfarin. *(More information)*
- The use of cholesterol-lowering medications called statins can decrease circulating coenzyme Q$_{10}$ concentrations. However, there is no evidence that this causes any adverse side effects in statin-treated patients. *(More information)*

Introduction

Coenzyme Q$_{10}$ is a member of the ubiquinone family of compounds. All animals, including humans, can synthesize ubiquinones, hence, coenzyme Q$_{10}$ is not considered a vitamin (1). The name ubiquinone refers to the ubiquitous presence of these compounds in living organisms and their chemical structure, which contains a functional group known as a benzoquinone. Ubiquinones are fat-soluble molecules with anywhere from 1 to 12 isoprene (5-carbon) units. The ubiquinone found in humans, ubidecaquinone or coenzyme Q$_{10}$, has a "tail" of 10 isoprene units (a total of 50 carbon atoms) attached to its benzoquinone "head" (**Figure 1**) (1).

Figure 1. The Different Redox Forms of Coenzyme Q$_{10}$



Coenzyme Q$_{10}$ exists in three oxidation states: the fully reduced ubiquinol form (CoQ$_{10}$H$_2$), the radical semiquinone intermediate (CoQ$_{10}$H·), and the fully oxidized ubiquinone form (CoQ$_{10}$).

[Figure 1 - Click to Enlarge]

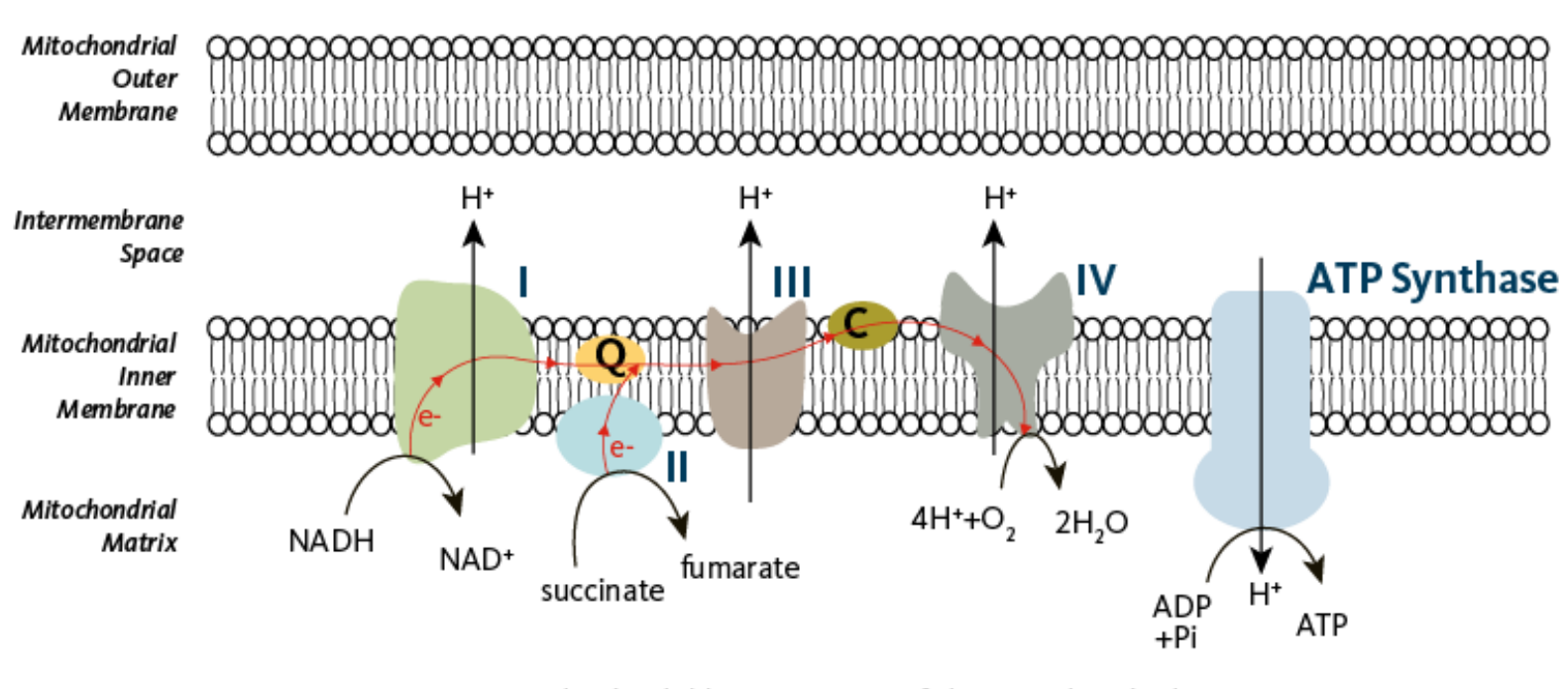
Biological Activities

Coenzyme Q$_{10}$ is soluble in lipids (fats) and is found in virtually all cell membranes, including mitochondrial membranes. The ability of the benzoquinone head group of coenzyme Q$_{10}$ to accept and donate electrons is a critical feature to its function. Coenzyme Q$_{10}$ can exist in three oxidation states (**Figure 1**): (i) the fully reduced ubiquinol form, CoQ$_{10}$H$_2$; (ii) the radical semiquinone intermediate, CoQ$_{10}$H·; and (iii) the fully oxidized ubiquinone form, CoQ$_{10}$.

Mitochondrial ATP synthesis

The conversion of energy from carbohydrates and fats to ATP, the form of energy used by cells, requires the presence of coenzyme Q$_{10}$ in the inner mitochondrial membrane. As part of the mitochondrial electron transport chain, coenzyme Q$_{10}$ accepts electrons from reducing equivalents generated during fatty acid and glucose metabolism and then transfers them to electron acceptors. At the same time, coenzyme Q$_{10}$ contributes to transfer protons (H$^+$) from the mitochondrial matrix to the intermembrane space, creating a proton gradient across the inner mitochondrial membrane. The energy released when the protons flow back into the mitochondrial interior is used to form ATP (**Figure 2**) (1). In addition to its role in ATP synthesis, mitochondrial coenzyme Q$_{10}$ mediates the oxidation of dihydroorotate to orotate in the *de novo* pyrimidine synthesis.

Figure 2. Mitochondrial Electron Transport Chain



Coenzyme Q$_{10}$ is a lipid-soluble component of the mitochondrial inner membrane that is critical to electron transport (in red) in the mitochondrial respiratory chain. Coenzyme Q$_{10}$ carries electrons from complexes I and II to complex III, thus participating in ATP production. *C, cytochrome C; e-, electron; H$^+$, proton; Q, coenzyme Q$_{10}$.*

[Figure 2 - Click to Enlarge]

Lysosomal function

Lysosomes are organelles within cells that are specialized for the digestion of cellular debris. The digestive enzymes within lysosomes function optimally at an acidic pH, meaning they require a permanent supply of protons. The lysosomal membranes that separate those digestive enzymes from the rest of the cell contain relatively high concentrations of coenzyme Q$_{10}$. Research suggests that coenzyme Q$_{10}$ plays an important role in the transport of protons across lysosomal membranes to maintain the optimal pH (2, 3).

Antioxidant functions

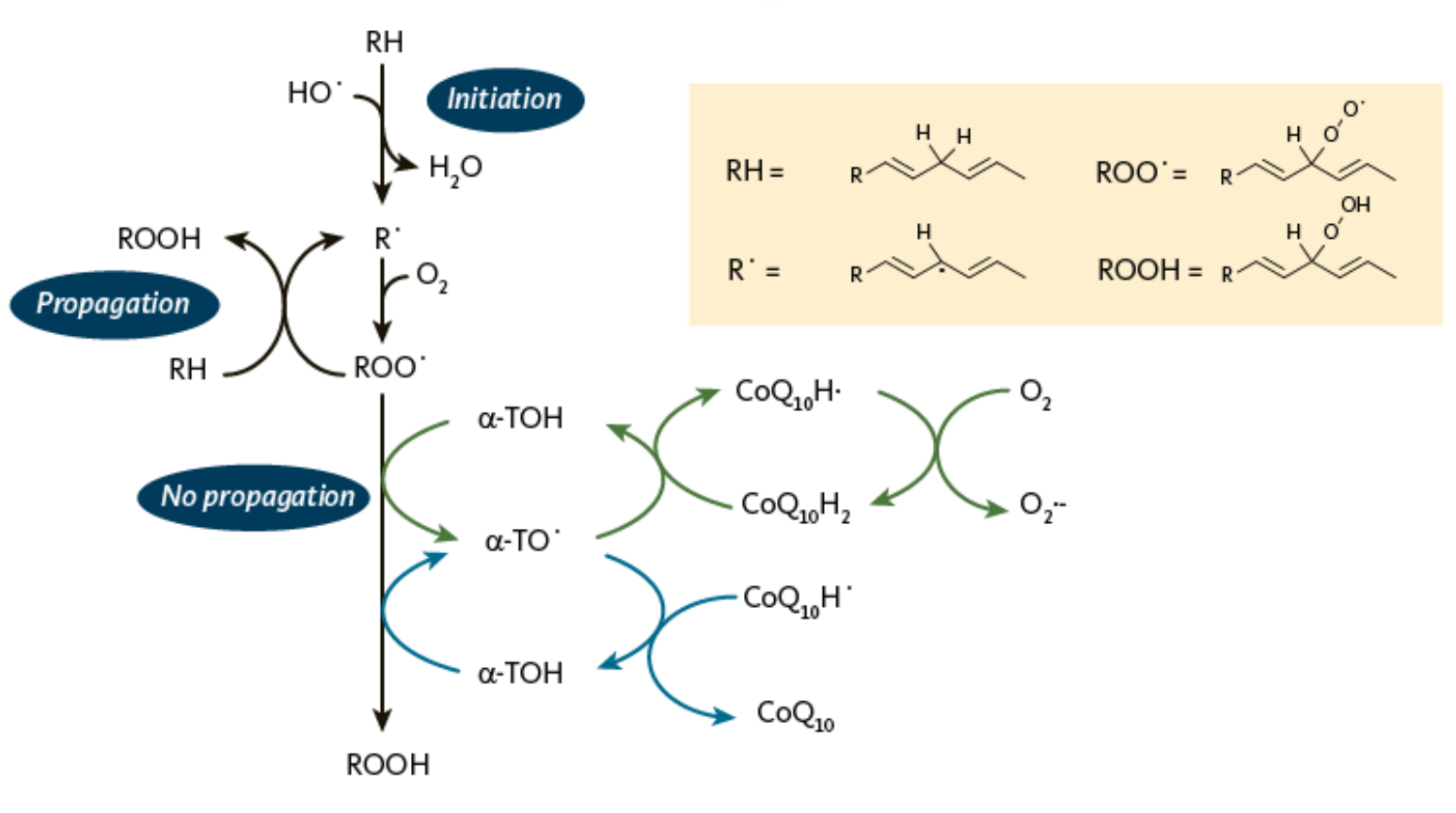
In its reduced form (CoQ$_{10}$H$_2$), coenzyme Q$_{10}$ is an effective fat-soluble antioxidant that protects cell membranes and lipoproteins from oxidation. The presence of a significant amount of CoQ$_{10}$H$_2$ in cell membranes, along with enzymes capable of reducing oxidized CoQ$_{10}$ back to CoQ$_{10}$H$_2$ (i.e., NAD(P)H oxidoreductases), supports the idea that CoQ$_{10}$H$_2$ is an important cellular antioxidant (4). CoQ$_{10}$H$_2$ has been found to inhibit lipid peroxidation when cell membranes and low-density lipoproteins (LDL) are exposed to oxidizing conditions. When LDL is oxidized, CoQ$_{10}$H$_2$ is the first antioxidant consumed. In isolated mitochondria, coenzyme Q$_{10}$ can protect membrane proteins and mitochondrial DNA from the oxidative damage that accompanies lipid peroxidation (5). Moreover, when present, CoQ$_{10}$H$_2$ was found to limit the formation of oxidized lipids and the consumption of α-tocopherol (a form of vitamin E with antioxidant properties) (6). Indeed, in addition to neutralizing free radicals directly, CoQ$_{10}$H$_2$ is capable of regenerating antioxidants like α-tocopherol and ascorbate (vitamin C) (4). Finally, the role of coenzyme Q$_{10}$ as an antioxidant is also exemplified by recent evidence showing that mitochondrial coenzyme Q$_{10}$ deficiency causes an increased production of mitochondrial superoxide radical anion ($O_2^{\bullet-}$) which might be driving insulin resistance in adipose and muscle tissues (7).

Nutrient interactions

Vitamin E

α-Tocopherol (vitamin E) and coenzyme Q$_{10}$ are the principal fat-soluble antioxidants in membranes and lipoproteins. When α-tocopherol (α-TOH) neutralizes a free radical, such as a lipid peroxyl radical (LOO·), it becomes oxidized itself, forming α-TO·, which can in turn promote the oxidation of lipoproteins under certain conditions in the test tube, thus propagating a chain reaction. However, when the reduced form of coenzyme Q$_{10}$ (CoQ$_{10}$H$_2$) reacts with α-TO·, α-TOH is regenerated and the semiquinone radical (CoQ$_{10}$H·) is formed. It is possible for CoQ$_{10}$H· to react with oxygen (O$_2$) to produce superoxide anion radical ($O_2^{\cdot -}$), which is a less reactive pro-oxidant than LOO·. However, CoQ$_{10}$H· can also reduce α-TO· back to α-TOH, resulting in the formation of fully oxidized coenzyme Q$_{10}$ (CoQ$_{10}$), which does not react with O$_2$ to form $O_2^{\cdot -}$ (**Figure 3**) (6, 8).

Figure 3. Antioxidant Activity of Coenzyme Q$_{10}$



The peroxidation of unsaturated lipids leads to the formation of lipid peroxyl radicals (ROO˙) that easily diffuse in biological systems. Peroxyl radicals react 1,000 times faster with α-tocopherol than with unsaturated lipids (RH). The hydroxyl group in the chromanol head of α-tocopherol (reduced form, α-TOH) can donate hydrogen to scavenge lipid peroxyl radicals, which halts their propagation in membranes and circulating lipoproteins. The presence of other antioxidants, such as coenzyme Q$_{10}$ (ubiquinol), is required to regenerate the antioxidant capacity of α-tocopherol.

In green: when the reduced form of coenzyme Q$_{10}$ (CoQ$_{10}$H$_2$) reacts with α-TO (oxidized α-tocopherol), α-TOH is regenerated and the semiquinone radical (ubisemiquinone, CoQ$_{10}$H˙) is formed. CoQ$_{10}$H˙ can react with oxygen (O$_2$) and produce superoxide ($O_2^{\cdot -}$), which is a much less oxidizing radical than ROO˙.

In blue: alternatively, CoQH˙ can also reduce α-TO˙ back to α-TOH, resulting in the formation of CoQ$_{10}$ (fully oxidized coenzyme Q$_{10}$ form), which does not react with O$_2$ to form superoxide.

[Figure 3 - Click to Enlarge]

Deficiency

Coenzyme Q$_{10}$ deficiency has not been described in the general population, so it is generally assumed that normal biosynthesis, with or without a varied diet, provides sufficient coenzyme Q$_{10}$ to sustain energy production in healthy individuals (9).

Primary coenzyme Q$_{10}$ deficiency is a rare genetic disorder caused by mutations in genes involved in coenzyme Q$_{10}$ biosynthetic pathway. To date, mutations in at least nine of these genes have been identified (1). As a result, primary coenzyme Q$_{10}$ deficiency is a clinically heterogeneous disorder that includes five major phenotypes: (i) severe infantile multi-systemic disease, (ii) encephalomyopathy, (iii) cerebellar ataxia, (iv) isolated myopathy, and (v) nephrotic syndrome. Whereas most mitochondrial respiratory chain disorders are hardly amenable to treatments, oral coenzyme Q$_{10}$ supplementation has been shown to improve muscular symptoms in some (yet not all) patients with primary coenzyme Q$_{10}$ deficiency (10). Neurological symptoms in patients with cerebellar ataxia are only partially relieved by coenzyme Q$_{10}$ (CoQ$_{10}$H$_2$) supplementation (10).

Secondary coenzyme Q$_{10}$ deficiency results from mutations or deletions in genes that are not directly related to coenzyme Q$_{10}$ biosynthetic pathway. Evidence of secondary coenzyme Q$_{10}$ deficiency has been reported in several mitochondrial disorders, such as mitochondrial DNA depletion syndrome, Kearns-Sayre syndrome, or multiple acyl-CoA dehydrogenase deficiency (MADD) (10). Secondary coenzyme Q$_{10}$ deficiency has also been identified in non-mitochondrial disorders, such as cardiofaciocutaneous syndrome and Niemann-Pick-type C disease (11). Because the therapeutic potential of supplemental coenzyme Q$_{10}$ is limited to its capacity to restore electron transfer in a defective mitochondrial respiratory chain and/or to increase antioxidant defense, patients with secondary coenzyme Q$_{10}$ deficiency may fail to respond to supplementation (see Disease Treatment).

Coenzyme Q$_{10}$ concentrations have been found to decline gradually with age in a number of different tissues (5, 12), but it is unclear whether this age-associated decline constitutes a deficiency (see Disease Prevention) (13). Decreased plasma concentrations of coenzyme Q$_{10}$ have been observed in individuals with diabetes mellitus, cancer, and congestive heart failure (see Disease Treatment). Lipid-lowering medications that inhibit the activity of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase (statins), a critical enzyme in both cholesterol and coenzyme Q$_{10}$ biosynthesis, decrease plasma coenzyme Q$_{10}$ concentrations (see HMG-CoA reductase inhibitors [statins]), although it remains unproven that this has any clinical implications.

Disease Prevention

Aging

According to the free radical and mitochondrial theories of aging, oxidative damage of cell structures by reactive oxygen species (ROS) plays an important role in the functional declines that accompany aging (14). ROS are generated by mitochondria as a byproduct of ATP production. If not neutralized by antioxidants, ROS may damage mitochondria over time, causing them to function less efficiently and to generate more damaging ROS in a self-perpetuating cycle. Coenzyme Q$_{10}$ plays an important role in mitochondrial ATP synthesis and functions as an antioxidant in mitochondrial membranes (see Biological Activities). One of the hallmarks of aging is a decline in energy metabolism in many tissues, especially liver, heart, and skeletal muscle. Tissue concentrations of coenzyme Q$_{10}$ have been found to decline with age, thereby accompanying age-related declines in energy metabolism (12). Early animal studies have not been able to demonstrate an effect of lifelong dietary supplementation with coenzyme Q$_{10}$ on the lifespan of rats or mice (15-17). Nonetheless, more recent studies have suggested that supplemental coenzyme Q$_{10}$ could promote mitochondrial biogenesis and respiration (18, 19) and delay senescence in transgenic mice (19). Presently, there is limited scientific evidence to suggest that coenzyme Q$_{10}$ supplementation prolongs life or prevents age-related functional declines in humans. In a small randomized controlled trial, elderly individuals (>70 years) who received a combination of selenium (100 μg/day) and coenzyme Q$_{10}$ (200 mg/day) for four years reported an improvement in vitality, physical performance, and quality of life (20). Further, a 12-year follow-up of these participants showed a reduction in cardiovascular mortality with supplemental selenium and coenzyme Q$_{10}$ compared to placebo (21).

Atherosclerosis

Oxidative modification of low-density lipoproteins (LDL) in arterial walls is thought to represent an early event leading to the development of atherosclerosis. Reduced coenzyme Q$_{10}$ (CoQ$_{10}$H$_2$) inhibits the oxidation of LDL in the test tube (*in vitro*) and works together with α-tocopherol (α-TOH) to inhibit LDL oxidation by regenerating α-TO· back to α-TOH. In the absence of a co-antioxidant, such as CoQ$_{10}$H$_2$ or vitamin C, α-TO· can, under certain conditions, promote the oxidation of LDL *in vitro* (6). Supplementation with coenzyme Q$_{10}$ increases the concentration of CoQ$_{10}$H$_2$ in human LDL (22). Studies in apolipoprotein E-deficient mice, an animal model of atherosclerosis, found that coenzyme Q$_{10}$ supplementation with supra-pharmacological amounts of coenzyme Q$_{10}$ inhibited lipoprotein oxidation in the blood vessel wall and the formation of atherosclerotic lesions (23). Interestingly, co-supplementation of these mice with α-TOH and coenzyme Q$_{10}$ was more effective in inhibiting atherosclerosis than supplementation with either α-TOH or coenzyme Q$_{10}$ alone (24).

Another important step in the development of atherosclerosis is the recruitment of immune cells known as monocytes into the blood vessel walls. This recruitment is dependent in part on monocyte expression of cell adhesion molecules (integrins). Supplementation of 10 healthy men and women with 200 mg/day of coenzyme Q$_{10}$ for 10 weeks resulted in significant decreases in monocyte expression of integrins, suggesting another potential mechanism for the inhibition of atherosclerosis by coenzyme Q$_{10}$ (25). Although coenzyme Q$_{10}$ supplementation shows promise as an inhibitor of LDL oxidation and atherosclerosis, more research is needed to determine whether coenzyme Q$_{10}$ supplementation can inhibit the development or progression of atherosclerosis in humans.

Disease Treatment

Primary and secondary coenzyme Q$_{10}$ deficiencies

Inherited coenzyme Q$_{10}$ deficiencies are rare diseases that are clinically and genetically heterogeneous (see Deficiency). In individuals with primary coenzyme Q$_{10}$ deficiency, early treatment with high-dose coenzyme Q$_{10}$ supplementation (10–30 mg/kg/day in children and 1.2–3.0 g/day in adults) may improve the pathological phenotype, yet the effectiveness depends on the type of mutations affecting the coenzyme Q$_{10}$ biosynthetic pathway (1, 26). Early treatment with pharmacological doses of coenzyme Q$_{10}$ is essential to limit irreversible organ damage in coenzyme Q$_{10}$-responsive deficiencies (1).

It is not clear to what extent coenzyme Q$_{10}$ supplementation might have therapeutic benefit in patients with inherited secondary Q$_{10}$ deficiencies. For example, multiple acyl-CoA dehydrogenase deficiency (MADD), caused by mutations in genes that impair the activity of enzymes involved in the transfer of electrons from acyl-CoA to coenzyme Q$_{10}$, is usually responsive to riboflavin monotherapy yet patients with low coenzyme Q$_{10}$ concentrations might also benefit from co-supplementation with coenzyme Q$_{10}$ and riboflavin (27). Another study suggested clinical improvements in secondary coenzyme Q$_{10}$ deficiency with supplemental coenzyme Q$_{10}$ in patients presenting with ataxia (28). Because the cause of secondary coenzyme Q$_{10}$ in inherited conditions is generally unknown, it is difficult to predict whether improving coenzyme Q$_{10}$ status with supplemental coenzyme Q$_{10}$ would lead to clinical benefits for the patients.

Finally, coenzyme Q$_{10}$ deficiency can be secondary to the inhibition of HMG-CoA reductase by statin drugs (see Deficiency). A 2015 meta-analysis of six small, randomized controlled trials found no reduction in statin-induced muscle pain with 100 to 400 mg/day of supplemental coenzyme Q$_{10}$ for one to three months (29). The trials failed to establish a diagnosis of relative coenzyme Q$_{10}$ deficiency before the intervention started, hence limiting the conclusion of the meta-analysis. While statin therapy may not necessary lead to a reduction in circulating coenzyme Q$_{10}$ concentrations, further research needs to examine whether secondary coenzyme Q$_{10}$ deficiency might be predisposing patients to statin-induced myalgia (30).

Cardiovascular disease

Congestive heart failure

Impairment of the heart's ability to pump enough blood for all of the body's needs is known as congestive heart failure. In coronary heart disease (CHD), accumulation of atherosclerotic plaque in the coronary arteries may prevent parts of the cardiac muscle from getting adequate blood supply, ultimately resulting in heart damage and impaired pumping ability. Heart failure can also be caused by myocardial infarction, hypertension, diseases of the heart valves, cardiomyopathy, and congenital heart diseases. Because physical exercise increases the demand on the weakened heart, measures of exercise tolerance are frequently used to monitor the severity of heart failure. Echocardiography is also used to determine the left ventricular ejection fraction, an objective measure of the heart's pumping ability (31).

A study of 1,191 heart failure patients found that low plasma coenzyme Q$_{10}$ concentration was a good biomarker of advanced heart disease (32). A number of small intervention trials that administered supplemental coenzyme Q$_{10}$ to congestive heart failure patients have been conducted. A 2014 literature review identified seven small randomized controlled trials examining the effect of coenzyme Q$_{10}$ supplementation (60-200 mg/day for ≤3 months in most trials) in heart failure patients (33). Pooling data from some of the trials showed an increase in serum coenzyme Q$_{10}$ concentrations (three studies) but no effect on left ventricular ejection fraction (two studies) or exercise capacity (two studies) (33). However, a recent meta-analysis of 14 randomized, placebo-controlled trials in 2,149 participants with heart failure found that supplemental coenzyme Q$_{10}$ (30-300 mg/day) resulted in a 39% reduction in mortality (seven studies), improved exercise capacity (four studies), but had no effect on left ventricular ejection fraction (nine studies) compared to placebo (34).

A trial is presently being conducted to assess the value of supplemental coenzyme Q$_{10}$ and/or D-ribose in the treatment of congestive heart failure in patients with normal left ventricular ejection fraction (35).

Ischemia-reperfusion injury

The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction or during cardiac surgery. Increased generation of reactive oxygen species (ROS) when the heart muscle's oxygen supply is restored (reperfusion) might be an important contributor to myocardial damage occurring during ischemia-reperfusion (36). Pretreatment of animals with coenzyme Q$_{10}$ has been found to preserve myocardial function following ischemia-reperfusion injury by increasing ATP concentration, enhancing antioxidant capacity and limiting oxidative damage, regulating autophagy, and reducing cardiomyocyte apoptosis (37). Another potential source of ischemia-reperfusion injury is aortic clamping during some types of cardiac surgery, such as coronary artery bypass graft (CABG) surgery. Early placebo-controlled trials found that coenzyme Q$_{10}$ pretreatment (60-300 mg/day for 7-14 days prior to surgery) provided some benefit in short-term outcome measures after CABG surgery (38, 39). In a small randomized controlled trial in 30 patients, oral administration of coenzyme Q$_{10}$ for 7 to 10 days before CABG surgery reduced the need for mediastinal drainage, platelet transfusion, and positive inotropic drugs (e.g. dopamine) and the risk of arrhythmia within 24 hours post-surgery (40). In one trial that did not find preoperative coenzyme Q$_{10}$ supplementation to be of benefit, patients were treated with 600 mg of coenzyme Q$_{10}$ 12 hours prior to surgery (41), suggesting that preoperative coenzyme Q$_{10}$ treatment may need to commence at least one week prior to CABG surgery to improve surgical outcomes. The combined administration of coenzyme Q$_{10}$, lipoic acid, omega-3 fatty acids, magnesium orotate, and selenium at least two weeks before CABG surgery and four weeks after was examined in a randomized, placebo-controlled trial in 117 patients with heart failure (42). The treatment resulted in lower concentration of troponin-I (a marker of cardiac injury), shorter length of hospital stay, and reduced risk of postoperative transient cardiac dysfunction compared to placebo (42).

Although trials have included relatively few people and examined mostly short-term, post-surgical outcomes, the results are promising (43).

Periprocedural myocardial injury

Coronary angioplasty (also called percutaneous coronary intervention) is a nonsurgical procedure for treating obstructive coronary heart disease, including unstable angina pectoris, acute myocardial infarction, and multivessel coronary heart disease. Angioplasty involves temporarily inserting and inflating a tiny balloon into the clogged artery to help restore the blood flow to the heart. Periprocedural myocardial injury that occurs in up to one-third of patients undergoing otherwise uncomplicated angioplasty increases the risk of morbidity and mortality at follow-up.

A prospective cohort study followed 55 patients with acute ST segment elevation myocardial infarction (a type of heart attack characterized by the death of some myocardial tissue) who underwent angioplasty (44). Plasma coenzyme Q$_{10}$ concentration one month after angioplasty was positively correlated with less inflammation and oxidative stress and predicted favorable left ventricular end-systolic volume remodeling at six months (44). One randomized controlled trial has examined the effect of coenzyme Q$_{10}$ supplementation on periprocedural myocardial injury in patients undergoing coronary angioplasty (45). The administration of 300 mg of coenzyme Q$_{10}$ 12 hours before the angioplasty to 50 patients reduced the concentration of C-reactive protein ([CRP]; a marker of inflammation) within 24 hours following the procedure compared to placebo. However, there was no difference in concentrations of two markers of myocardial injury (creatine kinase and troponin-I) or in the incidence of major adverse cardiac events one month after angioplasty between active treatment and placebo (45). Additional trials are needed to examine whether coenzyme Q$_{10}$ therapy can improve clinical outcomes in patients undergoing coronary angioplasty.

Angina pectoris

Myocardial ischemia may also lead to chest pain known as angina pectoris. People with angina pectoris often experience symptoms when the demand for oxygen exceeds the capacity of the coronary circulation to deliver it to the heart muscle, e.g., during exercise. Five small placebo-controlled studies have examined the effects of oral coenzyme Q$_{10}$ supplementation (60-600 mg/day) in addition to conventional medical therapy in patients with chronic stable angina (46). In most of the studies, coenzyme Q$_{10}$ supplementation improved exercise tolerance and reduced or delayed electrocardiographic changes associated with myocardial ischemia compared to placebo. However, only two of the studies found significant decreases in symptom frequency and use of nitroglycerin with coenzyme Q$_{10}$ supplementation. Presently, there is only limited evidence suggesting that coenzyme Q$_{10}$ supplementation would be a useful adjunct to conventional angina therapy.

Hypertension

Very few high-quality trials have examined the potential therapeutic benefit of coenzyme Q$_{10}$ supplementation in the treatment of primary hypertension (47). A systematic review identified two small randomized, double-blind, placebo-controlled trials that found little evidence of a reduction in systolic or diastolic blood pressure following the administration of coenzyme Q$_{10}$ (100-200 mg/day) for three months (47). In contrast, a meta-analysis that used less stringent selection criteria included 17 small trials and found evidence of a blood pressure-lowering effect of coenzyme Q$_{10}$ in patients with cardiovascular disease or metabolic disorders (48). The effect of coenzyme Q$_{10}$ on blood pressure needs to be examined in large, well-designed clinical trials.

Cardiovascular risk factors

Endothelial dysfunction: Normally functioning vascular endothelium promotes blood vessel relaxation (vasodilation) when needed (for example, during exercise) and inhibits the formation of blood clots. Atherosclerosis is associated with impairment of vascular endothelial function, thereby compromising vasodilation and normal blood flow. Endothelium-dependent vasodilation is impaired in individuals with elevated serum cholesterol concentrations, as well as in patients with coronary heart disease or diabetes mellitus. A 2012 meta-analysis examining the results of five small randomized controlled trials in 194 subjects in total found that supplemental coenzyme Q$_{10}$ (150-300 mg/day for 4 to 12 weeks) resulted in a clinically significant, 1.7% increase in flow-dependent endothelial-mediated dilation (49). Evidence from larger studies is needed to further establish the effect of coenzyme Q$_{10}$ on endothelium-dependent vasodilation.

Inflammation: Several small randomized controlled trials in patients at increased cardiovascular disease risk or with established cardiovascular disease have examined the effect of supplemental coenzyme Q$_{10}$ for ≤3 months on circulating inflammation markers i.e., CRP, interleukin-6, and/or tumor necrosis factor-α. Recently published pooled analyses of these trials have given mixed results (50-52). Larger studies are needed to examine the effect of coenzyme Q$_{10}$ supplementation on low-grade inflammation.

Blood lipids: Elevated plasma lipoprotein(a) concentration is an independent risk factor for cardiovascular disease. A meta-analysis of six controlled trials (of which five were randomized) in 409 participants found a reduction in plasma lipoprotein(a) concentration with coenzyme Q$_{10}$ supplementation (100-300 mg/day for 4-12 weeks) (53). Other effects of coenzyme Q$_{10}$ on blood lipids have not been reported (51, 53, 54).

A therapeutic approach combining coenzyme Q$_{10}$ with other antioxidants might prove to be more effective to target co-existing metabolic disorders in individuals at risk for cardiovascular disease (55).

Diabetes mellitus

Diabetes mellitus is a condition of increased oxidative stress and impaired energy metabolism. Plasma concentrations of reduced coenzyme Q$_{10}$ (CoQ$_{10}$H$_2$) have been found to be lower in diabetic patients than healthy controls after normalization to plasma cholesterol concentrations (56, 57). Randomized controlled trials that examined the effect of coenzyme Q$_{10}$ supplementation found little evidence of benefits on glycemic control in patients with diabetes mellitus. A meta-analysis of six trials in participants with type 2 diabetes and one trial in participants with type 1 diabetes found that 100 to 200 mg/day of coenzyme Q$_{10}$ for three to six months lowered neither fasting plasma glucose nor levels of glycated hemoglobin ([HbA1c]; a measure of glycemic control). Maternally inherited diabetes mellitus-deafness syndrome (MIDD) is caused by a mutation in mitochondrial DNA, which is inherited exclusively from one's mother. MIDD accounts for less than 1% of all cases of diabetes. Some early evidence suggested that long-term coenzyme Q$_{10}$ supplementation (150 mg/day) may improve insulin secretion and prevent progressive hearing loss in these patients (58, 59).

Of note, the pathogenesis of type 2 diabetes mellitus involves the early onset of glucose intolerance and hyperinsulinemia associated with the progressive loss of tissue responsiveness to insulin. Recent experimental studies tied insulin resistance to a decrease in coenzyme Q$_{10}$ expression and showed that supplementation with coenzyme Q$_{10}$ could restore insulin sensitivity (7). Coenzyme Q$_{10}$ supplementation might thus be a more useful tool for the primary prevention of type 2 diabetes rather than for its management.

Neurodegenerative diseases

Parkinson's disease

Parkinson's disease is a degenerative neurological disorder characterized by tremors, muscular rigidity, and slow movements. It is estimated to affect approximately 1% of Americans over the age of 65. Mitochondrial dysfunction and oxidative damage in a part of the brain called the substantia nigra may play a role in the development of the disease (60). Decreased ratios of reduced-to-oxidized coenzyme Q$_{10}$ have been found in platelets of individuals with Parkinson's disease (61, 62). One study also found higher concentrations of oxidized coenzyme Q$_{10}$ in the cerebrospinal fluid of patients with untreated Parkinson's disease compared to healthy controls (63). Additionally, a study in postmortem Parkinson's disease patients found lower concentrations of total coenzyme Q$_{10}$ in the cortex region of the brain compared to age-matched controls, but no differences were seen in other brain areas, including the striatum, substantia nigra, and cerebellum (64).

A 16-month randomized, placebo-controlled phase II clinical trial evaluated the safety and efficacy of 300, 600, or 1,200 mg/day of coenzyme Q$_{10}$ in 80 people with early Parkinson's disease (65). Coenzyme Q$_{10}$ supplementation was well tolerated at all doses and resulted in a slower deterioration of function in Parkinson's disease patients in the group taking 1,200 mg/day. A phase III clinical trial was then designed to further examine the effect of high-dose coenzyme Q$_{10}$ (1,200-2,400 mg/day) and vitamin E (1,200 IU/day) supplementation on both motor and non-motor symptoms associated with Parkinson's disease. This trial was prematurely terminated because it was unlikely that such a treatment was effective in treating Parkinson's disease (66). A smaller placebo-controlled trial showed that oral administration of 300 mg/day of coenzyme Q$_{10}$ for 48 to 96 months moderately improved motor symptoms in treated patients (with Levodopa) with re-emerging symptoms but not in patients at an early stage of the disease (67). Two recent meta-analyses of randomized, placebo-controlled trials found no evidence that coenzyme Q$_{10}$ improved motor-related symptoms or delayed the progression of the disease when compared to placebo (68, 69).

Huntington's disease

Huntington's disease is an inherited neurodegenerative disorder characterized by selective degeneration of nerve cells known as striatal spiny neurons. Symptoms, such as movement disorders and impaired cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. Animal models indicate that impaired mitochondrial function and glutamate-mediated neurotoxicity may be involved in the pathology of Huntington's disease. Some, but not all, studies in mouse models of Huntington's disease have suggested that coenzyme Q$_{10}$ supplementation could improve motor performance, overall survival, and various hallmarks of Huntington's disease, i.e., brain atrophy, ventricular enlargement, and striatal neuronal atrophy (70, 71). Interestingly, co-administration of coenzyme Q$_{10}$ with remacemide (an NMDA receptor antagonist), the antibiotic minocycline, or creatine led to greater improvements in most biochemical and behavioral parameters (70-72).

To date, only two clinical trials have examined whether coenzyme Q$_{10}$ might be efficacious in human patients with Huntington's disease. A 30-month, randomized, placebo-controlled trial of coenzyme Q$_{10}$ (600 mg/day), remacemide, or both in 347 patients with early Huntington's disease found that neither coenzyme Q$_{10}$ nor remacemide significantly altered the decline in total functional capacity, although coenzyme Q$_{10}$ supplementation (with or without remacemide) resulted in a nonsignificant trend toward a slower decline (73). A 20-week pilot trial examined the safety and tolerability of increasing dosages of coenzyme Q$_{10}$ (1,200 mg/day, 2,400 mg/day, and 3,600 mg/day) in eight healthy subjects and in 20 patients with Huntington's disease; 22 of the subjects completed the study (74). All dosages were generally well tolerated, with gastrointestinal symptoms being the most frequently reported adverse effect. Blood concentrations of coenzyme Q$_{10}$ at the end of the study were maximized with the daily dose of 2,400 mg (74). This dose was tested in a multicenter phase III clinical trial in 609 participants with early-stage Huntington's disease. Participants were randomized to receive either 2,400 mg/day of coenzyme Q$_{10}$ or placebo for five years (75). The trial was prematurely halted because it appeared unlikely to demonstrate any health benefit in supplemented patients — about one-third of participants completed the trial at the time of study termination (75). Although coenzyme Q$_{10}$ is generally well tolerated, there is no evidence that supplementation can improve functional and cognitive symptoms in Huntington's disease patients.

Inherited ataxias

Friedreich's ataxia (FRDA): FRDA is an autosomal recessive neurodegenerative disease caused by mutations in the gene *FXN* that encodes for the mitochondrial protein, frataxin. Frataxin is needed for the making of iron-sulfur clusters (ISC). ISC-containing subunits are especially important for the mitochondrial respiratory chain and for the synthesis of heme-containing proteins (76). Frataxin deficiency is associated with imbalances in iron-sulfur containing proteins, mitochondrial respiratory chain dysfunction and lower ATP production, and accumulation of iron in the mitochondria, which increases oxidative stress and oxidative damage to macromolecules of the respiratory chain (77). Clinically, FRDA is a progressive disease characterized by ataxia, areflexia, speech disturbance (dysarthria), sensory loss, motor dysfunction, cardiomyopathy, diabetes, and scoliosis (77). A pilot study administering coenzyme Q$_{10}$ (200 mg/day) and vitamin E (2,100 IU/day) to 10 FDRA patients found that energy metabolism of cardiac and skeletal muscle was improved after only three months of therapy (78). Follow-up assessments at 47 months indicated that cardiac and skeletal muscle improvements were maintained and that FRDA patients showed significant increases in fractional shortening, a measure of cardiac function. Moreover, the therapy was effective at preventing the progressive decline of neurological function (79). Another study reported both coenzyme Q$_{10}$ and vitamin E deficiencies among FRDA patients and suggested that co-supplementation with both compounds, at doses as low as 30 mg/day of coenzyme Q$_{10}$ and 4 IU/day of vitamin E, might improve disease symptoms (80). Large-scale, randomized controlled trials are necessary to determine whether coenzyme Q$_{10}$, in conjunction with vitamin E, has therapeutic benefit in FRDA. At present, about one-half of patients use coenzyme Q$_{10}$ and vitamin E supplements despite the lack of proven therapeutic benefit (77).

Spinocerebellar ataxias (SCAs): SCAs are a group of rare autosomal dominant neurodegenerative diseases characterized by gait difficulty, loss of hand dexterity, dysarthria, and cognitive decline. SCA1, 2, 3, and 6 are the most common SCAs (81). *In vitro* coenzyme Q$_{10}$ treatment of forearm skin fibroblasts isolated from patients with SCA2 was found to reduce oxidative stress and normalize complex I and II-III activity of the mitochondrial respiratory chain (82). A multicenter prospective cohort study that followed 319 patients with SCAs (≥15 years) found no difference in the rate of disease progression over two years between those taking supplemental coenzyme Q$_{10}$ (median dose, 600 mg/day) and nonusers (81).

Cancer

Early interest in coenzyme Q$_{10}$ as a potential therapeutic agent in cancer was stimulated by an observational study that found that individuals with lung, pancreas, and especially breast cancer were more likely to have low plasma coenzyme Q$_{10}$ concentrations than healthy controls (83). Two randomized controlled trials have explored the effect of coenzyme Q$_{10}$ as an adjunct to conventional therapy for breast cancer. Supplementation with coenzyme Q$_{10}$ failed to improve measures of fatigue and quality of life in patients newly diagnosed with breast cancer (84) and in patients receiving chemotherapy (85).

Performance

Athletic performance

There is little evidence that supplementation with coenzyme Q$_{10}$ improves athletic performance in healthy individuals. A few placebo-controlled trials have examined the effects of 100 to 150 mg/day of supplemental coenzyme Q$_{10}$ for three to eight weeks on physical performance in trained and untrained men. Most did not find significant differences between the group taking coenzyme Q$_{10}$ and the group taking placebo with respect to measures of aerobic exercise performance, such as maximal oxygen consumption (VO$_2$ max) and exercise time to exhaustion (86-90). One study found the maximal cycling workload to be slightly (4%) increased after eight weeks of coenzyme Q$_{10}$ supplementation compared to placebo, although measures of aerobic power were not increased (91). Two studies actually found significantly greater improvement in measures of anaerobic (87) and aerobic (86) exercise performance with a placebo than with supplemental coenzyme Q$_{10}$. More recent studies have suggested that coenzyme Q$_{10}$ could help reduce both muscle damage-associated oxidative stress and low-grade inflammation induced by strenuous exercise (92-95). Studies on the effect of supplementation on physical performance in women are lacking, but there is little reason to suspect a gender difference in the response to coenzyme Q$_{10}$ supplementation.

Sources

Biosynthesis

Coenzyme Q$_{10}$ is synthesized in most human tissues. The biosynthesis of coenzyme Q$_{10}$ involves three major steps: (1) synthesis of the benzoquinone structure from 4-hydroxybenzoate derived from either tyrosine or phenylalanine, two amino acids; (2) synthesis of the polyisoprenoid side chain from acetyl-coenzyme A (CoA) via the mevalonate pathway; and (3) the joining (condensation) of these two structures to form coenzyme Q$_{10}$. In the mevalonate pathway, the enzyme 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, which converts HMG-CoA into mevalonate, is common to the biosynthetic pathways of both coenzyme Q$_{10}$ and cholesterol and is inhibited by statins (cholesterol-lowering drugs; see Drug interactions) (1).

Of note, pantothenic acid (formerly vitamin B$_5$) is the precursor of coenzyme A, and pyridoxine (vitamin B$_6$), in the form of pyridoxal-5'-phosphate, is required for the conversion of tyrosine to 4-hydroxyphenylpyruvic acid that constitutes the first step in the biosynthesis of the benzoquinone structure of coenzyme Q$_{10}$. It is not known to what extent the coenzyme Q$_{10}$ biosynthetic pathway may be affected by inadequate pantothenic acid and/or vitamin B$_6$ nutritional status.

Food sources

It has been estimated that dietary consumption contributes to about 25% of plasma coenzyme Q$_{10}$, but there are currently no specific dietary intake recommendations for coenzyme Q$_{10}$ from the US National Academy of Medicine (formerly the Institute of Medicine) or other agencies (96). The extent to which dietary consumption contributes to tissue coenzyme Q$_{10}$ concentrations is not clear.

Based on studies employing food frequency questionnaires, the average dietary intake of coenzyme Q$_{10}$ is about 3 to 6 mg/day (97). Rich sources of dietary coenzyme Q$_{10}$ include mainly meat, poultry, and fish. Other good sources include soybean, corn, olive, and canola oils; nuts; and seeds. Fruit, vegetables, eggs, and dairy products are moderate sources of coenzyme Q$_{10}$ (97). Some dietary sources are listed in **Table 1**.

Table 1. Coenzyme Q$_{10}$ Content of Selected Foods (98-100)

Food	Serving	Coenzyme Q$_{10}$ (mg)
Beef, fried	3 ounces*	2.6
Herring, marinated	3 ounces	2.3
Chicken, fried	3 ounces	1.4
Soybean oil	1 tablespoon	1.3
Canola oil	1 tablespoon	1.0
Rainbow trout, steamed	3 ounces	0.9
Peanuts, roasted	1 ounce	0.8
Sesame seeds, roasted	1 ounce	0.7
Pistachio nuts, roasted	1 ounce	0.6
Broccoli, boiled	½ cup, chopped	0.5
Cauliflower, boiled	½ cup, chopped	0.4
Orange	1 medium	0.3
Strawberries	½ cup	0.1
Egg, boiled	1 medium	0.1
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Supplements

Coenzyme Q$_{10}$ is available without a prescription as a dietary supplement in the US. Doses in supplements for adults range from 30 to 100 mg/day, which are considerably higher than typically estimated dietary coenzyme Q$_{10}$ intakes. Coenzyme Q$_{10}$ is fat-soluble and is best absorbed with fat in a meal. Doses higher than 100 mg/day are generally divided into two or three doses throughout the day (101). Less than 5% of orally administered coenzyme Q$_{10}$ is thought to reach the circulation (102). Therefore, pharmacological doses of coenzyme Q$_{10}$ as high as 1,200 to 3,000 mg/day for adults and 30 mg/kg/day for children are usually needed to relieve symptoms in patients with coenzyme Q$_{10}$ deficiency (26).

Does oral coenzyme Q$_{10}$ supplementation increase tissue concentrations?

Oral supplementation with coenzyme Q$_{10}$ is known to increase blood and lipoprotein concentrations of coenzyme Q$_{10}$ in humans (2, 15, 22). Plasma coenzyme Q$_{10}$ appears to reach a plateau following supplementation with a dose of 2,400 mg/day (103, 104). Yet, under normal circumstances, uptake of supplemental coenzyme Q$_{10}$ from peripheral tissues/organs is likely limited because coenzyme Q$_{10}$ is ubiquitously synthesized (105). Nonetheless, under certain physiological circumstances (e.g., aging) or in pathologies, coenzyme Q$_{10}$ status might be compromised and it is then presumed that supplementation might increase coenzyme Q$_{10}$ concentrations in tissues that are deficient (106). For example, a study in 24 older adults supplemented with 300 mg/day of coenzyme Q$_{10}$ or placebo for at least seven days prior to cardiac surgery found that the coenzyme Q$_{10}$ content of atrial tissue was significantly increased in those taking coenzyme Q$_{10}$, especially in patients greater than 70 years of age (38). In another study of patients with left ventricular dysfunction, supplementation with 150 mg/day of coenzyme Q$_{10}$ for four weeks before cardiac surgery increased coenzyme Q$_{10}$ concentrations in the heart but not in skeletal muscle (107). Finally, a 2007 review of the literature highlighted that plasma coenzyme Q$_{10}$ concentrations higher than 'normal' were likely needed to promote coenzyme Q$_{10}$ uptake by peripheral tissues and different tissues may indeed require different plasma thresholds for the uptake of coenzyme Q$_{10}$ (102).

Safety

Toxicity

There have been no reports of significant adverse side effects of oral coenzyme Q$_{10}$ supplementation at doses as high as 3,000 mg/day for up to eight months (103), 1,200 mg/day for up to 16 months (65), and 600 mg/day for up to 30 months (73). According to the observed safe level (OSL) risk assessment method, evidence of safety is strong with doses up to 1,200 mg/day of coenzyme Q$_{10}$ (108). Some people have experienced gastrointestinal symptoms, such as nausea, diarrhea, appetite suppression, heartburn, and abdominal discomfort, especially with daily doses ≥200 mg (109). These adverse effects may be minimized if daily doses >100 mg are divided into two or three daily doses (101). During pregnancy, the use of coenzyme Q$_{10}$ supplements (100 mg twice daily) from 20 weeks' gestation was found to be safe (110). Because reliable data in lactating women are not available, supplementation should be avoided during breast-feeding (110).

Drug interactions

Warfarin

Concomitant use of warfarin (Coumadin) and coenzyme Q$_{10}$ supplements has been reported to decrease the anticoagulant effect of warfarin in a few cases (111). An individual on warfarin should not begin taking coenzyme Q$_{10}$ supplements without consulting the health care provider who is managing his or her anticoagulant therapy. If warfarin and coenzyme Q$_{10}$ are to be used concomitantly, blood tests to assess clotting time (prothrombin time; PT/INR) should be monitored frequently, especially in the first two weeks.

HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase is an enzyme that catalyzes a biochemical reaction that is common to both cholesterol and coenzyme Q$_{10}$ biosynthetic pathways (see Biosynthesis). Statins are HMG-CoA reductase inhibitors that are widely used as cholesterol-lowering medications. Statins can thus also reduce the endogenous synthesis of coenzyme Q$_{10}$. Therapeutic use of statins, including simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor, Altocor, Altoprev), rosuvastatin (Crestor), and atorvastatin (Lipitor), has been shown to decrease circulating coenzyme Q$_{10}$ concentrations (112-121). However, because coenzyme Q$_{10}$ circulates with lipoproteins, plasma coenzyme Q$_{10}$ concentration is influenced by the concentration of circulating lipids (122, 123). It is likely that circulating coenzyme Q$_{10}$ concentrations are decreased because statins reduce circulating lipids rather than because they inhibit coenzyme Q$_{10}$ synthesis (124). In addition, very few studies have examined coenzyme Q$_{10}$ concentrations in tissues other than blood such that the extent to which statin therapy affects coenzyme Q$_{10}$ concentrations in the body's tissues is unknown (118, 120, 125). Finally, there is currently little evidence to suggest that secondary coenzyme Q$_{10}$ deficiency is responsible for statin-associated muscle symptoms in treated patients. In addition, supplementation with coenzyme Q$_{10}$ failed to relieve myalgia in statin-treated patients (see Disease Treatment) (126, 127).

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Lipoic Acid

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日本語

Summary

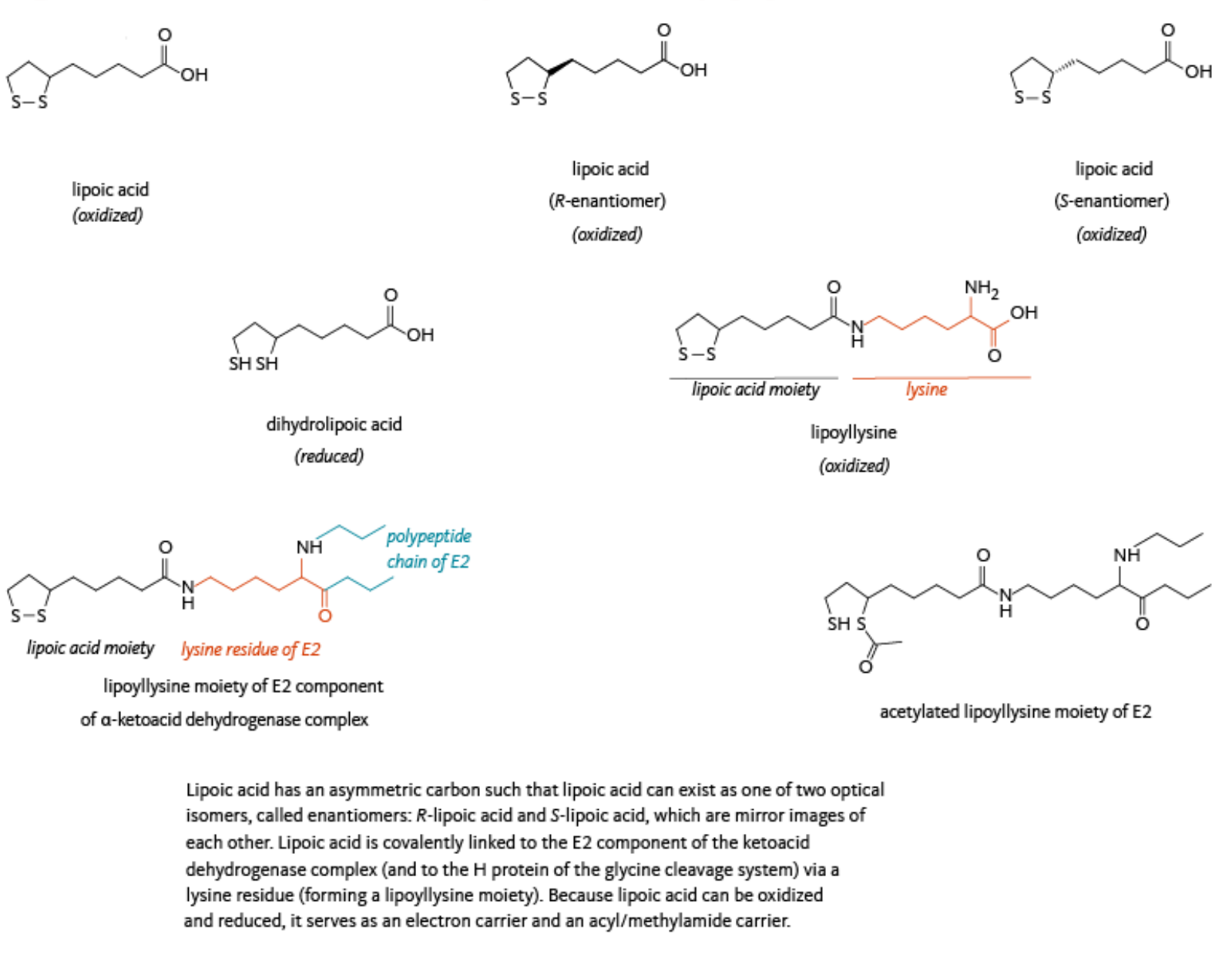
- Lipoic acid (often called α-lipoic acid), also known as thioctic acid, is a naturally occurring compound that is also synthesized by humans. (More information)
- Endogenously synthesized lipoic acid is bound to protein and functions as a cofactor for several important mitochondrial multienzyme complexes. (More information)
- Supplementation with lipoic acid transiently increases plasma and cellular concentrations of unbound lipoic acid. (More information)
- Lipoic acid is a direct antioxidant, although any increase in radical scavenging activity *in vivo* is likely transient. Lipoic acid may also trigger antioxidant defense, enhance cellular glucose uptake, and modulate the activity of various cell-signaling molecules and transcription factors. (More information)
- Some evidence from small randomized controlled studies suggests that high-dose lipoic acid may improve measures of glucose utilization in subjects with metabolic disorders. (More information)
- Available evidence suggests that treatment with intravenous or oral lipoic acid may help reduce symptoms of diabetic peripheral neuropathy. It is important to note that many of the studies examining the efficacy of lipoic acid for the treatment of diabetic neuropathy have been conducted by one German research group and funded by the manufacturer of lipoic acid in Germany. (More information)
- Lipoic acid was found to slow disease progression when administered to a mouse model of multiple sclerosis. A two-year clinical trial designed to assess the effect of lipoic acid on loss of mobility and changes in brain volume in patients with progressive multiple sclerosis is ongoing. (More information)
- Current evidence is too limited to suggest whether lipoic acid supplementation could benefit patients with Alzheimer's disease. (More information)
- Supplementation with lipoic acid may show some benefits in terms of weight control for individuals with high body mass index. (More information)
- Lipoic acid occurs naturally in food covalently bound to protein, whereas supplements contain unbound (free) lipoic acid. If you choose to use supplements, the Linus Pauling Institute recommends a daily dose of 200 to 400 mg/day for generally healthy people. (More information)

Introduction

Lipoic acid (often called α-lipoic acid), also known as thioctic acid, is a naturally occurring organosulfur compound that is synthesized by plants and animals, including humans (1, 2). Lipoic acid is covalently bound to certain proteins, which function as part of essential mitochondrial multienzyme complexes involved in energy and amino acid metabolism (see Biological Activities). In addition to the physiological functions of protein-bound lipoic acid, there is increasing scientific and medical interest in potential therapeutic uses of pharmacological doses of free (unbound) lipoic acid (3).

Lipoic acid contains two thiol (sulfur) groups, which may be oxidized or reduced; dihydrolipoic acid is the reduced form of lipoic acid (**Figure 1**) (4). Lipoic acid also contains an asymmetric carbon, which means that lipoic acid can exist as one of two possible optical isomers, also called enantiomers. These enantiomers are mirror images of each other: *R*-lipoic acid and *S*-lipoic acid (**Figure 1**). Only the *R*-enantiomer is endogenously synthesized and covalently bound to protein. *R*-lipoic acid occurs naturally in food (see Food sources). Free (unbound) lipoic acid supplements may contain either *R*-lipoic acid or a 50:50 (racemic) mixture of *R*-lipoic acid and *S*-lipoic acid (see Supplements).

Figure 1. Chemical Structures of Lipoic Acid and Lipoyllysine Residue



Lipoic acid has an asymmetric carbon such that lipoic acid can exist as one of two optical isomers, called enantiomers: *R*-lipoic acid and *S*-lipoic acid, which are mirror images of each other. Lipoic acid is covalently linked to the E2 component of the ketoacid dehydrogenase complex (and to the H protein of the glycine cleavage system) via a lysine residue (forming a lipoyllysine moiety). Because lipoic acid can be oxidized and reduced, it serves as an electron carrier and an acyl/methylamide carrier.

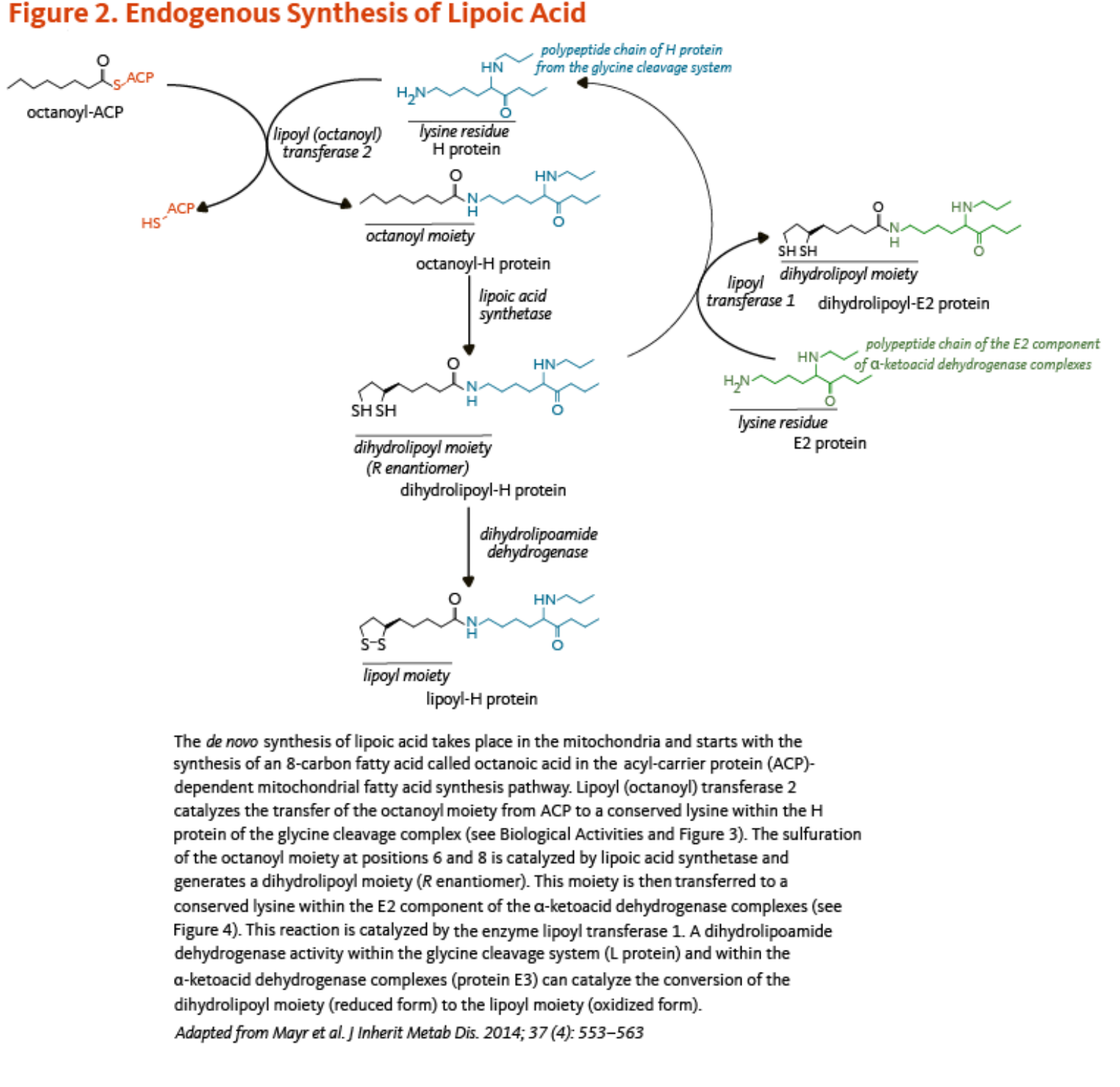
[Figure 1 - Click to Enlarge]

Metabolism and Bioavailability

Endogenous biosynthesis

The synthesis of lipoic acid has been characterized in detail in the yeast *Saccharomyces cerevisiae*, but not all genes involved in the process have been identified in humans (5). Lipoic acid is synthesized *de novo* in mitochondria from octanoic acid, an 8-carbon fatty acid (C8:0), bound to the acyl-carrier protein (ACP; see article on Pantothenic Acid) during the process of fatty acid synthesis (**Figure 2**). An enzyme called lipoyl (octanoyl) transferase 2 catalyzes the transfer of the octanoyl moiety from octanoyl-ACP to a conserved lysine of the H protein of the glycine cleavage system (see also Biological Activities). The next reaction is the insertion of two sulfur atoms at positions 6 and 8 of the protein H-bound octanoyl moiety, thereby producing a dihydrolipoyl moiety. This step is catalyzed by the lipoic acid synthetase (also called lipoyl synthase), an enzyme containing iron-sulfur clusters that act as sulfur donors in the reaction (5). Finally, the enzyme lipoyl transferase 1 catalyzes the transfer of the dihydrolipoyl moiety from the H protein of the glycine cleavage system to conserved lysine residues of the E2 components of the α-ketoacid dehydrogenase multienzyme complexes (5). The oxidation of the dihydrolipoyl moiety is catalyzed by a dihydrolipoamide dehydrogenase (**Figure 2**).

Figure 2. Endogenous Synthesis of Lipoic Acid



The *de novo* synthesis of lipoic acid takes place in the mitochondria and starts with the synthesis of an 8-carbon fatty acid called octanoic acid in the acyl-carrier protein (ACP)-dependent mitochondrial fatty acid synthesis pathway. Lipoyl (octanoyl) transferase 2 catalyzes the transfer of the octanoyl moiety from ACP to a conserved lysine within the H protein of the glycine cleavage complex (see Biological Activities and Figure 3). The sulfuration of the octanoyl moiety at positions 6 and 8 is catalyzed by lipoic acid synthetase and generates a dihydrolipoyl moiety (*R* enantiomer). This moiety is then transferred to a conserved lysine within the E2 component of the α-ketoacid dehydrogenase complexes (see Figure 4). This reaction is catalyzed by the enzyme lipoyl transferase 1. A dihydrolipoamide dehydrogenase activity within the glycine cleavage system (L protein) and within the α-ketoacid dehydrogenase complexes (protein E3) can catalyze the conversion of the dihydrolipoyl moiety (reduced form) to the lipoyl moiety (oxidized form).
Adapted from Mayr et al. J Inherit Metab Dis. 2014; 37 (4): 553–563

[Figure 2 - Click to Enlarge]

Dietary and supplemental lipoic acid

Consumption of lipoic acid from food has not yet been found to result in detectable increases of free lipoic acid in human plasma or cells (3, 6). In contrast, high oral doses of free lipoic acid (≥50 mg) significantly, yet transiently, increase the concentration of free lipoic acid in plasma and cells. Pharmacokinetic studies in humans have found that about 30%-40% of an oral dose of a racemic mixture of *R*-lipoic acid and *S*-lipoic acid is absorbed (6, 7). Oral lipoic acid supplements are better absorbed on an empty stomach than with food: taking lipoic acid with food (versus without food) decreased peak plasma lipoic acid concentrations by about 30% and total plasma lipoic acid concentrations by about 20% (8). A liquid formulation of *R*-lipoic acid was found to be better absorbed and more stable in the plasma, suggesting that it might be more efficacious than the solid form in the management of a condition like diabetic neuropathy (9, 10).

There may also be differences in bioavailability of the two isomers of lipoic acid. Following single oral doses *R,S*-lipoic acid (racemic mixture), peak plasma concentrations of *R*-lipoic acid were found to be 40%-50% higher than *S*-lipoic acid, suggesting a differential absorption in favor of the *R*-enantiomer (6, 8, 11). Yet, following oral ingestion, both enantiomers are rapidly metabolized and excreted. Plasma lipoic acid concentrations generally peak within one hour or less and decline rapidly (6, 7, 11, 12). In cells, lipoic acid is swiftly reduced to dihydrolipoic acid, and *in vitro* studies indicate that dihydrolipoic acid is then rapidly exported from cells (3). Moreover, a pilot study in 19 healthy adults suggested that the bioavailability of *R,S*-lipoic acid and *R*-lipoic acid may vary with age and gender (13).

Finally, there is no evidence in humans that exogenous lipoic acid can be 'activated' with ATP or GTP and incorporated into lipoic acid-dependent enzymes by a lipoyl transferase (14). As a consequence, a loss of lipoic acid-dependent enzymatic activity caused by defects in endogenous lipoic acid synthesis (see Deficiency) cannot be rescued by the provision of exogenous lipoic acid (5).

Biological Activities

Protein-bound lipoic acid

Enzyme cofactor

R-lipoic acid is an essential cofactor for several mitochondrial multienzyme complexes that catalyze critical reactions related to the catabolism (breakdown) of amino acids and the production of energy (15). *R*-lipoic acid is covalently bound to a specific lysine residue in at least one of the proteins in each multienzyme complex. Such a non-protein cofactor is known as a "prosthetic group."

R-lipoic acid functions as a prosthetic group for the biological activity of the following multienzyme complexes:

- The **glycine cleavage system** that catalyzes the decarboxylation of glycine coupled with the addition of a methylene group (-CH_2) to tetrahydrofolate to form 5,10-methylene tetrahydrofolate, an important cofactor in the synthesis of nucleic acids (**Figure 3**). Within the glycine cleavage system, *R*-lipoic acid is covalently bound to a conserved lysine of the H protein (**Figures 2 and 3**).
- Four α-ketoacid dehydrogenase complexes (**Figure 4**), including:

(i) the **pyruvate dehydrogenase complex** that catalyzes the conversion of pyruvate to acetyl-coenzyme A (CoA), an important substrate for energy production via the citric acid cycle;

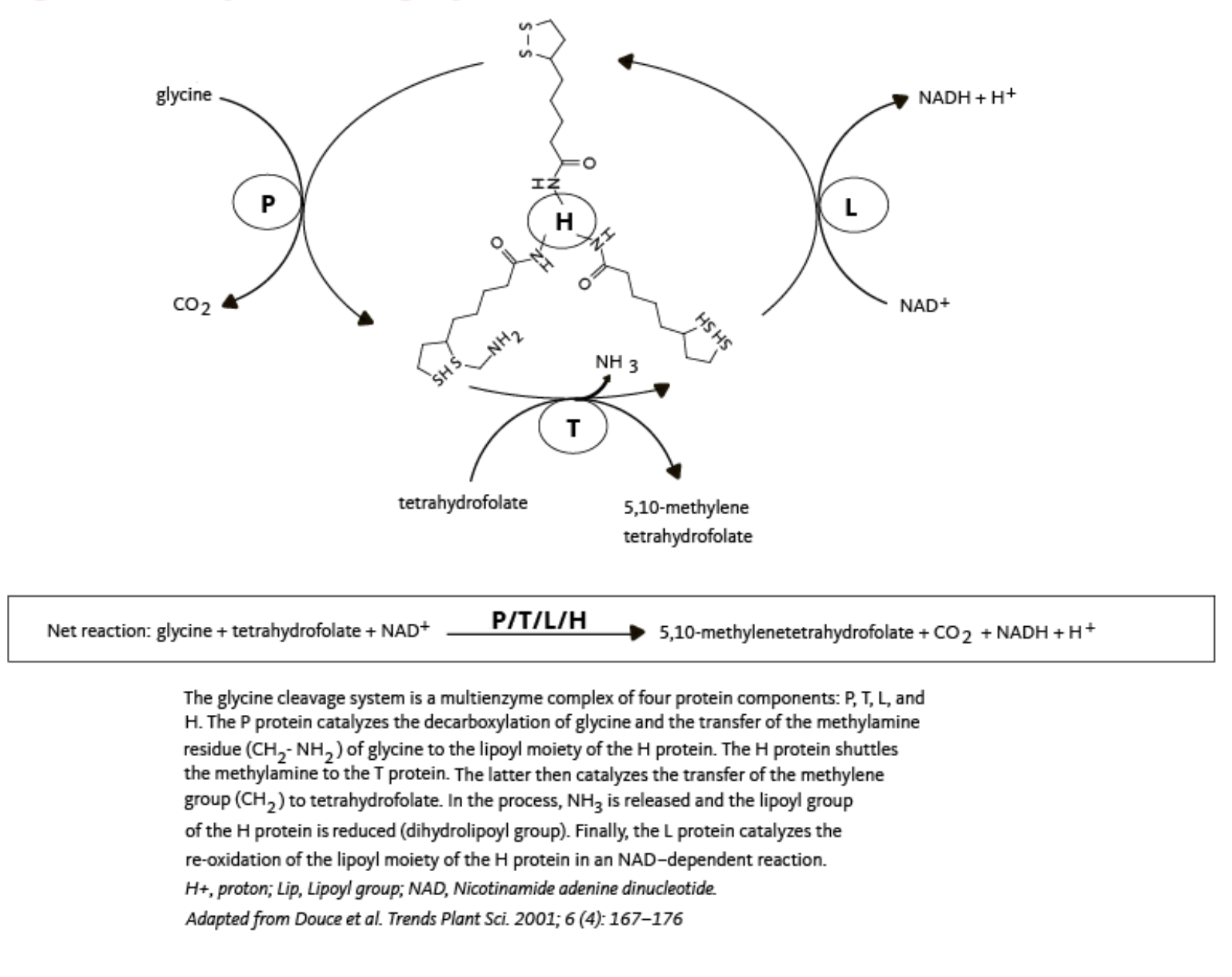
(ii) the **α-ketoglutarate dehydrogenase complex** that catalyzes the conversion of α-ketoglutarate to succinyl CoA, another important intermediate of the citric acid cycle;

(iii) the **branched-chain α-ketoacid dehydrogenase complex** that is involved in the decarboxylation of ketoacids in the catabolic pathway of the branched-chain amino acids, namely leucine, isoleucine, and valine;

(iv) the **2-oxoadipate dehydrogenase complex** that catalyzes the decarboxylation of 2-oxoadipate to glutaryl-CoA in the catabolic pathway of lysine, hydroxylysine, and tryptophan.

All four α-ketoacid dehydrogenase complexes contain three enzymatic activities, namely E1, E2, and E3. E1 is a thiamin pyrophosphate (TPP)-dependent α-ketoacid dehydrogenase, *R*-lipoic acid functions as a prosthetic group essential for E2 transacetylase activity, and E3 is a flavin adenine dinucleotide (FAD)-dependent dihydrolipoamide dehydrogenase (**Figure 4**). *R*-lipoic acid is also found in the E3-binding protein (protein X component) of the pyruvate dehydrogenase complex (5).

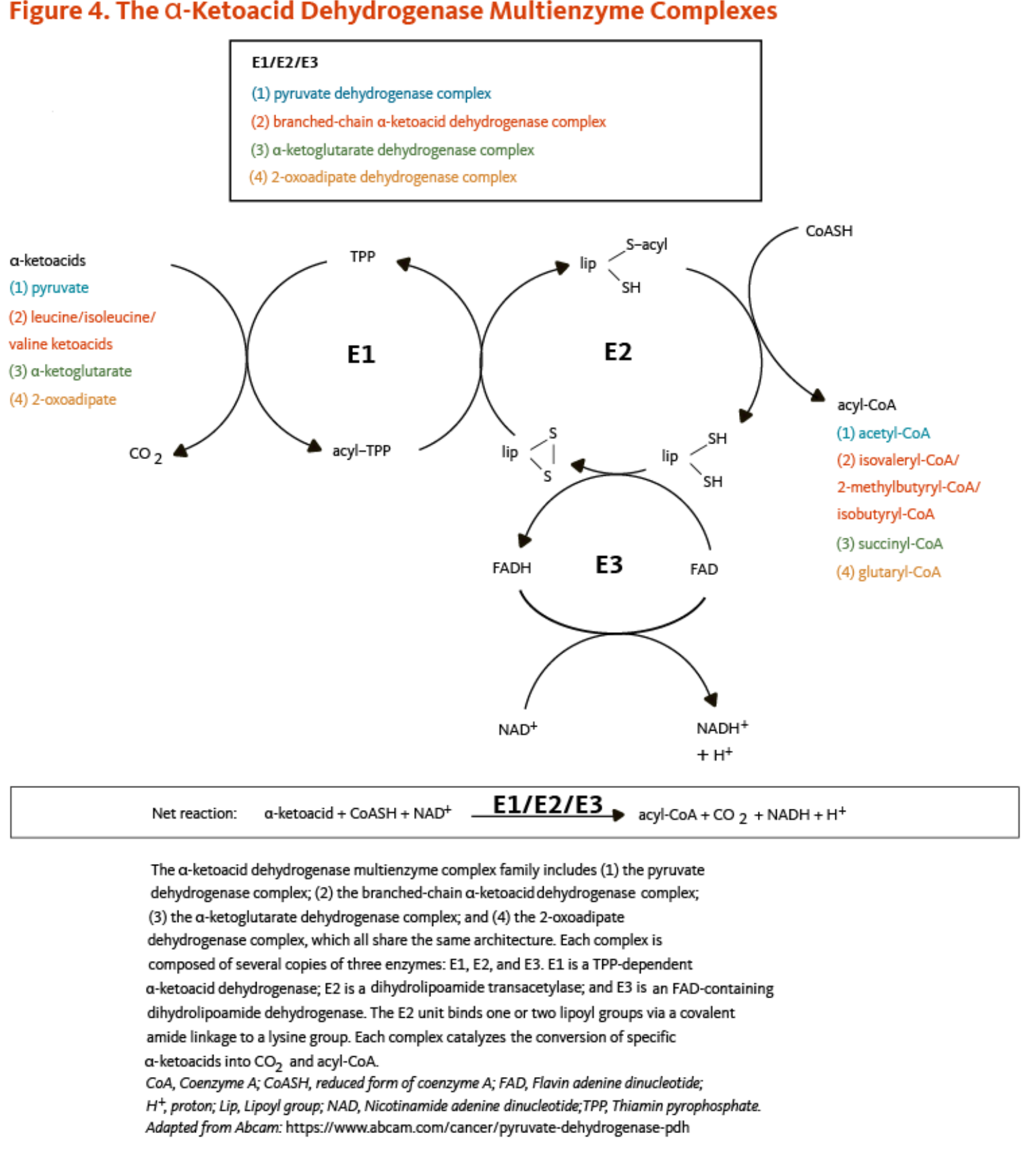
Figure 3. The Glycine Cleavage System


glycine
P
CO_2
H
NADH + H+
L
NAD+
NH_3
T
tetrahydrofolate
5,10-methylene tetrahydrofolate
Net reaction: glycine + tetrahydrofolate + NAD+ P/T/L/H 5,10-methylenetetrahydrofolate + CO_2 + NADH + H+

The glycine cleavage system is a multienzyme complex of four protein components: P, T, L, and H. The P protein catalyzes the decarboxylation of glycine and the transfer of the methylamine residue (CH_2- NH_2) of glycine to the lipoyl moiety of the H protein. The H protein shuttles the methylamine to the T protein. The latter then catalyzes the transfer of the methylene group (CH_2) to tetrahydrofolate. In the process, NH_3 is released and the lipoyl group of the H protein is reduced (dihydrolipoyl group). Finally, the L protein catalyzes the re-oxidation of the lipoyl moiety of the H protein in an NAD–dependent reaction.
H+, proton; Lip, Lipoyl group; NAD, Nicotinamide adenine dinucleotide.
Adapted from Douce et al. Trends Plant Sci. 2001; 6 (4): 167–176

[Figure 3 - Click to Enlarge]

Figure 4. The α-Ketoacid Dehydrogenase Multienzyme Complexes


E1/E2/E3
(1) pyruvate dehydrogenase complex
(2) branched-chain α-ketoacid dehydrogenase complex
(3) α-ketoglutarate dehydrogenase complex
(4) 2-oxoadipate dehydrogenase complex
α-ketoacids
(1) pyruvate
(2) leucine/isoleucine/valine ketoacids
(3) α-ketoglutarate
(4) 2-oxoadipate
CO_2
TPP
acyl–TPP
E1
E2
lip S–acyl SH
CoASH
acyl-CoA
(1) acetyl-CoA
(2) isovaleryl-CoA/2-methylbutyryl-CoA/isobutyryl-CoA
(3) succinyl-CoA
(4) glutaryl-CoA
lip
E3
FADH
FAD
NAD+
NADH+ + H+
Net reaction: α-ketoacid + CoASH + NAD+ E1/E2/E3 acyl-CoA + CO_2 + NADH + H+

The α-ketoacid dehydrogenase multienzyme complex family includes (1) the pyruvate dehydrogenase complex; (2) the branched-chain α-ketoacid dehydrogenase complex; (3) the α-ketoglutarate dehydrogenase complex; and (4) the 2-oxoadipate dehydrogenase complex, which all share the same architecture. Each complex is composed of several copies of three enzymes: E1, E2, and E3. E1 is a TPP-dependent α-ketoacid dehydrogenase; E2 is a dihydrolipoamide transacetylase; and E3 is an FAD-containing dihydrolipoamide dehydrogenase. The E2 unit binds one or two lipoyl groups via a covalent amide linkage to a lysine group. Each complex catalyzes the conversion of specific α-ketoacids into CO_2 and acyl-CoA.
CoA, Coenzyme A; CoASH, reduced form of coenzyme A; FAD, Flavin adenine dinucleotide; H+, proton; Lip, Lipoyl group; NAD, Nicotinamide adenine dinucleotide;TPP, Thiamin pyrophosphate.
Adapted from Abcam: https://www.abcam.com/cancer/pyruvate-dehydrogenase-pdh

[Figure 4 - Click to Enlarge]

Unbound lipoic acid

When considering the biological activities of supplemental (unbound) lipoic acid, it is important to keep in mind the limited and transient nature of the increases in plasma and tissue lipoic acid (see Metabolism and Bioavailability) (3).

Antioxidant activities

Scavenging reactive oxygen and nitrogen species: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are highly reactive compounds with the potential to damage DNA, proteins, and lipids in cell membranes. Both lipoic acid and dihydrolipoic acid can directly scavenge (neutralize) physiologically relevant ROS and RNS in the test tube (reviewed in 3). However, whether direct quenching reactions occur *in vivo* is unknown. The highest tissue concentrations of free lipoic acid likely to be achieved through oral supplementation are at least 10 times lower than those of other intracellular antioxidants, such as vitamin C and glutathione. Moreover, free lipoic acid is rapidly eliminated from cells, so any increases in direct radical scavenging activity are unlikely to be sustained.

Regeneration of other antioxidants: When an antioxidant scavenges a free radical, it becomes oxidized itself and is not able to scavenge additional ROS or RNS until it has been reduced. In the test tube, dihydrolipoic acid is a potent reducing agent with the capacity to reduce the oxidized forms of several important antioxidants, including coenzyme Q_{10}, vitamin C, and glutathione (**Figure 5**) (16, 17). Dihydrolipoic acid may also reduce the oxidized form of α-tocopherol (vitamin E) directly or indirectly through regenerating oxidized vitamin C (see the article on Vitamin E) (18) or oxidized coenzyme Q_{10} (see the article on Coenzyme Q_{10}) (19). Whether dihydrolipoic acid effectively regenerates antioxidants under physiological conditions is unclear (3).

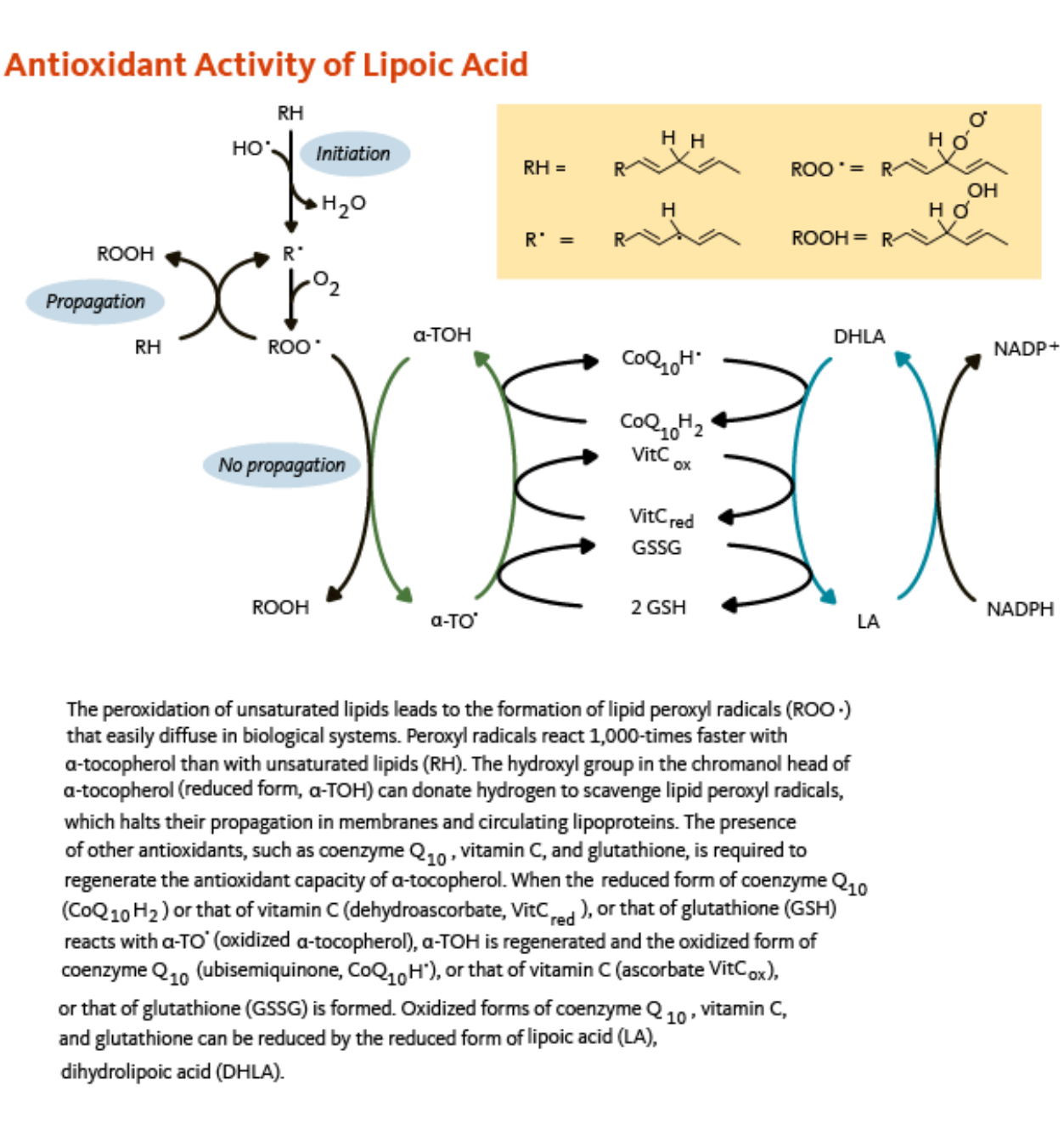
Metal chelation: Redox-active metal ions, such as free iron and copper, can induce oxidative damage by catalyzing reactions that generate highly reactive free radicals (20). Compounds that chelate free metal ions in a way that prevents them from generating free radicals offer promise in the treatment of neurodegenerative diseases and other chronic diseases in which metal-induced oxidative damage may play a pathogenic role (21). Both lipoic acid and dihydrolipoic acid have been found to inhibit copper- and iron-mediated oxidative damage in the test tube (22, 23) and to inhibit excess iron and copper accumulation in animal models (24, 25). Lipoic acid may also be helpful as an adjunct treatment against heavy metal toxicity. No clinical trial has examined the use of lipoic acid as a chelating agent in mercury toxicity, yet it has proven to be effective in several mammalian species (26, 27).

Activation of antioxidant signaling pathways: Glutathione is an important intracellular antioxidant that also plays a role in the detoxification and elimination of potential carcinogens and toxins. Reductions in glutathione synthesis and tissue glutathione concentrations in aged animals (compared to younger ones) are suggestive of a potentially lower ability to respond to oxidative stress or toxin exposure (28). Lipoic acid has been found to increase glutathione concentrations in cultured cells and in the tissues of aged animals fed lipoic acid (29, 30). Lipoic acid might be able to increase glutathione synthesis in aged rats by up-regulating the expression of γ-glutamylcysteine ligase (γ-GCL), the rate-limiting enzyme in glutathione synthesis (31), and by increasing cellular uptake of cysteine, an amino acid required for glutathione synthesis (32). Lipoic acid was found to upregulate the expression of γ-GCL and other antioxidant enzymes via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway (31, 33).

Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol. Keap1 responds to oxidative stress signals by freeing Nrf2. Upon release, Nrf2 translocates to the nucleus where it can bind to the antioxidant response element (ARE) located in the promoter region of genes coding for antioxidant enzymes and scavengers. Lipoic acid — but not dihydrolipoic acid — can react with specific sulfhydryl residues of Keap1, causing the release of Nrf2 (34). Nrf2/ARE target genes code for several mediators of the antioxidant response, including γ-GCL, NAD(P)H quinone oxidoreductase 1 (NQO-1), heme oxygenase-1 (HO-1), catalase, and superoxide dismutase (SOD). For example, the upregulation of the Nrf2 pathway by lipoic acid in cultured hepatocytes and in the liver of obese or diabetic rats prevented lipid overload-induced steatosis (35) and cell death (36). Lipoic acid also protected liver from oxidative stress-induced liver injury in methotrexate-treated rats through the activation of Nrf-2 pathway and other anti-inflammatory pathways (37). Pre-treatment and post-treatment with lipoic acid, respectively, prevented and reversed lipopolysaccharide (LPS)-induced lung histopathological alterations in rats through Nrf2-mediated HO-1 upregulation (38).

Inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX): NOX is a plasma membrane-bound enzymatic complex that catalyzes the production of superoxide from oxygen and NADPH and has been involved in innate immune defense against microbes (39). Lipoic acid prevented NOX-induced superoxide production in a rat model of cerebral ischemia and limited infarct volume and neurological deficiencies through upregulating the insulin-phosphatidylinositide-3 kinase (PI3K)-protein kinase B (PKB/Akt) signaling pathway (40). Treatment of gastric cancer cells with lipoic acid limited NOX-generated ROS production and reduced cancer cell proliferation induced by *Helicobacter pylori* (*H. pylori*) infection (41).

Figure 5. Antioxidant Activity of Lipoic Acid



The peroxidation of unsaturated lipids leads to the formation of lipid peroxyl radicals (ROO•) that easily diffuse in biological systems. Peroxyl radicals react 1,000-times faster with α-tocopherol than with unsaturated lipids (RH). The hydroxyl group in the chromanol head of α-tocopherol (reduced form, α-TOH) can donate hydrogen to scavenge lipid peroxyl radicals, which halts their propagation in membranes and circulating lipoproteins. The presence of other antioxidants, such as coenzyme Q_{10}, vitamin C, and glutathione, is required to regenerate the antioxidant capacity of α-tocopherol. When the reduced form of coenzyme Q_{10} ($CoQ_{10}H_2$) or that of vitamin C (dehydroascorbate, $VitC_{red}$), or that of glutathione (GSH) reacts with α-TO• (oxidized α-tocopherol), α-TOH is regenerated and the oxidized form of coenzyme Q_{10} (ubisemiquinone, $CoQ_{10}H^•$), or that of vitamin C (ascorbate $VitC_{ox}$), or that of glutathione (GSSG) is formed. Oxidized forms of coenzyme Q_{10}, vitamin C, and glutathione can be reduced by the reduced form of lipoic acid (LA), dihydrolipoic acid (DHLA).

[Figure 5 - Click to Enlarge]

Regulation of cellular glucose uptake

The binding of insulin to the insulin receptor stimulates a cascade of protein phosphorylations leading to the translocation of glucose transporters (GLUT4) to the cell membrane and an increased cellular uptake of glucose (3, 42). Lipoic acid has been found to activate the insulin signaling cascade in cultured cells (3, 42, 43), increase GLUT4 translocation to cell membranes, and increase glucose uptake in cultured adipose and muscle cells (44, 45). A computer modeling study suggested that lipoic acid might bind to the intracellular tyrosine kinase domain of the insulin receptor and stabilize the active form of the enzyme (43).

Regulation of other signaling pathways

In addition to Nrf2 and insulin signaling pathways, lipoic acid was found to target other cell-signaling molecules thereby affecting a variety of cellular processes, including metabolism, stress responses, proliferation, and survival. For example, in cultured endothelial cells, lipoic acid was found to inhibit IKK-β, an enzyme that promotes the translocation of redox-sensitive and pro-inflammatory transcription factor, nuclear factor-kappa B (NFκB) from the cytosol to the nucleus (46). Lipoic acid has also been shown to improve nitric oxide (NO)-dependent vasodilation in aged rats by increasing PKB/Akt-dependent phosphorylation of endothelial NO synthase (eNOS) and eNOS-catalyzed NO production (47). Additionally, lipoic acid increased mitochondrial biogenesis through triggering AMP-activated protein kinase (AMPK)-induced transcription factor PGC-1α activation in skeletal muscle of aged mice (48). Several reviews of the literature have described pathways that are potential targets of lipoic acid in various models and under different experimental conditions (49-52).

Deficiency

Lipoic acid deficiency has been described in rare cases of inherited mutations in the lipoic acid biosynthetic pathway. Mutations identified in patients with defective lipoic acid metabolism affect genes involved in the synthesis of iron-sulfur clusters and genes coding for lipoic acid synthetase (*LIAS*), lipoyl transferase 1 (*LIPT1*), and dihydrolipoamide dehydrogenase (E3 component of α-ketoacid dehydrogenase complexes; *DLD*) (5, 53, 54).

Disease Treatment

Diabetes mellitus

Chronically elevated blood glucose concentration is the hallmark of diabetes mellitus. Type 1 diabetes is caused by the autoimmune destruction of the insulin-producing β-cells of the pancreas, leading to an insufficient production of insulin. Exogenous insulin is required to maintain a normal blood glucose concentration (i.e., fasting blood glucose <100 milligram per deciliter [mg/dL]). In contrast, impaired tissue glucose uptake in response to insulin (a phenomenon called insulin resistance) plays a key role in the development of type 2 diabetes (55). Although patients with type 2 diabetes may eventually require insulin, interventions that enhance insulin sensitivity may be used to maintain normal blood glucose concentrations. The term 'prediabetes' is sometimes used to describe early metabolic abnormalities that place individuals at high risk of developing type 2 diabetes. Of note, these patients are also at high risk for cardiovascular disease. According to the American Diabetes Association, prediabetes can be defined by a condition of impaired fasting glucose, characterized by a fasting blood glucose concentration between 100 mg/dL and 125 mg/dL and/or a condition of impaired glucose tolerance, characterized by a 2-hour blood glucose concentration ≥140 mg/dL following an oral glucose tolerance test (56).

Glucose utilization

The effect of high-dose lipoic acid on glucose utilization has been primarily examined in individuals with type 2 diabetes. An early clinical trial in 13 patients with type 2 diabetes found that a single intravenous infusion of 1,000 mg of lipoic acid improved insulin-stimulated glucose disposal (i.e., insulin sensitivity) by 50% compared to a placebo infusion (57). A placebo-controlled study of 72 patients with type 2 diabetes found that oral administration of lipoic acid at doses of 600 mg/day, 1,200 mg/day or 1,800 mg/day improved insulin sensitivity by 25% after four weeks of treatment (58). There were no significant differences among the three doses of lipoic acid, suggesting that 600 mg/day may be the maximum effective dose (55). However, in a more recent randomized, placebo-controlled study in 102 subjects, daily supplementation with 600 mg of lipoic acid (+/- 800 mg of vitamin E [α-tocopherol]) for 16 weeks had no effect on fasting blood glucose, fasting blood insulin, or a measure of insulin resistance called the homeostatic model assessment of insulin resistance (HOMA-IR) index (59). A 2018 systematic review and meta-analysis identified 20 randomized controlled trials (published between 2007 and 2017) that examined the effect of supplemental lipoic acid on markers of glucose utilization in 1,245 subjects with metabolic disorders (not limited to type 2 diabetes) (60). Administration of lipoic acid (200 to 1,800 mg/day for 2 weeks to 1 year), alone or together with other nutrients, was found to lower fasting blood glucose and insulin concentrations, insulin resistance, and blood HbA1c concentration — a marker of glycemic control over the past few months (60).

Endothelial function

The inner lining of blood vessels, known as the vascular endothelium, plays an important role in the maintenance of cardiovascular health. In particular, nitric oxide (NO) regulates vascular tone and blood flow by promoting the relaxation of all types of blood vessels, including arteries — a phenomenon called vasodilation. Alterations in NO-mediated endothelium-dependent vasodilation results in widespread vasoconstriction and coagulation abnormalities and is considered to be an early step in the development of atherosclerosis. The presence of chronic hyperglycemia, insulin resistance, oxidative stress, and pro-inflammatory mechanisms contribute to endothelial dysfunction in patients with diabetes mellitus (61).

The measurement of brachial flow-mediated dilation (FMD) is often used as a surrogate marker of endothelial function. Two techniques are being used to measure endothelium-dependent vasodilation. One technique measures the forearm blood flow by venous occlusion plethysmography during infusion of acetylcholine. Using this invasive technique, intra-arterial infusion of lipoic acid was found to improve endothelium-dependent vasodilation in 39 subjects with type 2 diabetes but not in 11 healthy controls (62). A more recent randomized, double-blind, placebo-controlled study in 30 patients with type 2 diabetes found that intravenous infusion of 600 mg of lipoic acid improved the response to the endothelium-dependent vasodilator acetylcholine but not to the endothelium-independent vasodilator, glycerol trinitrate (63). Another noninvasive technique using ultrasound to measure flow-mediated vasodilation was used in two additional studies conducted by Xiang et al. (64, 65). The results of these randomized, placebo-controlled studies showed that intravenous lipoic acid could improve endothelial function in patients with impaired fasting glucose (64) or impaired glucose tolerance (65).

One randomized placebo-controlled trial that assessed the effect of oral lipoic acid supplementation in 58 patients diagnosed with metabolic syndrome, a condition characterized by abnormal glucose and lipid metabolism, showed that flow-mediated vasodilation improved by 44% with 300 mg/day of lipoic acid for four weeks (66).

Diabetic neuropathy

Peripheral neuropathy: Up to 50% of diabetic patients develop peripheral neuropathy, a type of nerve damage that may result in pain, loss of sensation, and weakness, particularly in the lower extremities (67). Peripheral neuropathy is also a leading cause of lower limb amputation in diabetic patients (68). Several mechanisms have been proposed to explain chronic hyperglycemia-induced nerve damage, such as intracellular accumulation of sorbitol, glycation reactions, and oxidative and nitrosative stress (reviewed in 69). The results of several large randomized controlled trials indicated that maintaining blood glucose at near normal concentrations was the most important step in limiting the risk of diabetic neuropathy and lower extremity amputation (70-72). However, evidence of the efficacy of enhanced control of glycemia in preventing neuropathy is stronger in patients with type 1 diabetes than in those with type 2 diabetes (73). Moreover, this glucose control intervention increased the risk of hypoglycemic episodes (73).

The efficacy of lipoic acid, administered either intravenously or orally, in the management of neuropathic symptoms has been examined in patients with diabetes. Meta-analyses of randomized controlled trials suggest that infusion of 300 to 600 mg/day of lipoic acid for two to four weeks significantly reduced the symptoms of diabetic neuropathy to a clinically meaningful degree (55, 74). Regarding the efficacy of oral lipoic acid supplementation, an initial short-term study in 24 patients with type 2 diabetes mellitus found that the symptoms of peripheral neuropathy improved in those who took 600 mg of lipoic acid three times a day for three weeks compared to those who took a placebo (75). A larger clinical trial randomly assigned more than 500 patients with type 2 diabetes and symptomatic peripheral neuropathy to one of the following treatments: (i) 600 mg/day of intravenous lipoic acid for three weeks followed by 1,800 mg/day of oral lipoic acid for six months, (ii) 600 mg/day of intravenous lipoic acid for three weeks followed by oral placebo for six months, or (iii) intravenous placebo for three weeks followed by oral placebo for six months (76). Evidence of improvements in sensory and motor deficits — assessed by physicians — could be observed after three weeks of intravenous lipoic acid therapy, yet not at the end of six months of oral lipoic acid therapy. However, another randomized, double-blind, placebo-controlled trial in 181 patients with diabetic neuropathy found that oral supplementation with either 600 mg/day, 1,200 mg/day, or 1,800 mg/day of lipoic acid for five weeks significantly improved neuropathic symptoms (77). In this study, the 600 mg/day dose was as effective as the higher doses. Finally, a four-year, multicenter, clinical trial in 421 diabetic patients with distal symmetric sensorimotor polyneuropathy found no difference between oral administration of 600 mg/day of lipoic and placebo on the primary endpoint, a composite score that assessed neuropathic impairment of the lower limbs and nerve conduction (78). Yet, measures of specific neuropathic impairments (secondary outcomes) improved with lipoic acid supplementation (78). A post-hoc analysis suggested that oral lipoic acid supplementation may reduce neuropathic symptoms particularly in subjects with a high burden of cardiovascular disease, diabetes, and neuropathy yet with normal body mass index (BMI) and blood pressure (79).

Autonomic neuropathy: Another neuropathic complication of diabetes mellitus is cardiac autonomic neuropathy (CAN), which occurs in as many as 25% of diabetic patients (55). CAN is characterized by damage to the nerve fibers that innervate the heart and blood vessels, leading to reduced heart rate variability (variability in the time interval between heartbeats) and increased risk of mortality (80). In a randomized controlled trial of 72 patients with type 2 diabetes and reduced heart rate variability, oral supplementation with 800 mg/day of lipoic acid for four months resulted in significant improvement in two out of four measures of heart rate variability compared to placebo (81).

Summary: Overall, the available research suggests that treatment with intravenous or oral lipoic acid may help reduce symptoms of diabetic peripheral neuropathy. The use of lipoic acid is currently approved for the treatment of diabetic neuropathy in Germany (4). It is important to note that many of the studies that examined the efficacy of lipoic acid in the treatment of diabetic neuropathy have been primarily conducted by one German research group and funded by the manufacturer of lipoic acid in Germany (82).

Diabetic retinopathy

Chronic hyperglycemia can damage blood vessels in the retina and cause a potentially sight-threatening condition called diabetic retinopathy (83). One placebo-controlled study examined the effect of lipoic acid on the visual capability of 80 participants of whom 12 had type 1 diabetes, 48 had type 2 diabetes, and 20 were diabetes-free. The result showed that daily oral administration of 300 mg of lipoic acid for three months prevented the deterioration of contrast sensitivity in patients with diabetes and improved it in healthy patients compared to placebo (84).

Multiple sclerosis

Multiple sclerosis is an autoimmune disease of unknown etiology that is characterized by the progressive destruction of myelin and nerve fibers in the central nervous system, causing neurological symptoms in affected individuals (85). There are four main types of multiple sclerosis defined according to the disease course: (i) clinically isolated syndrome, (ii) relapsing-remitting multiple sclerosis, (iii) secondary progressive multiple sclerosis, and (iv) primary progressive multiple sclerosis (for more information, visit the National Multiple Sclerosis Society website) (86). Lipoic acid was found to effectively slow disease progression when administered either orally (87), intraperitoneally (88), or subcutaneously (89) to mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. *In vitro* and animal studies have found that lipoic acid exhibits immunomodulatory properties through mechanisms that stimulate the production of cyclic AMP (cAMP) (90, 91) — a central regulator of innate immune functions — and inhibits the migration of immune cells into the brain and spinal cord (92), possibly by decreasing endothelial expression of cell adhesion molecules, inhibiting expression of enzymes like matrix metalloproteinases (MMP), and/or reducing the permeability of the blood-brain barrier (87, 89, 93, 94).

Only a few studies have examined lipoic acid supplementation in humans. A small pilot study designed to evaluate the safety of lipoic acid in 30 people with relapsing or progressive multiple sclerosis found that treatment with 1,200 to 2,400 mg/day of oral lipoic acid for two weeks was generally well tolerated (see Safety) (95). In this study, higher serum concentrations of lipoic acid were associated with the lowest serum concentrations of MMP-9 — a marker of inflammation (95). Another study suggested that an oral dose of 1,200 mg of lipoic acid in subjects with multiple sclerosis could help achieve serum lipoic acid concentrations similar to those found to be therapeutic in mice (96). A randomized, placebo-controlled study in 52 subjects (mean age, 30 years) with relapsing-remitting multiple sclerosis found an increase in total antioxidant capacity in blood with lipoic acid supplementation (1,200 mg/day for 12 weeks) yet not in the activity of specific antioxidant enzymes (superoxide dismutase and glutathione peroxidase) (97). Supplemental lipoic acid also decreased the serum concentrations of some (IFN-γ, ICAM-1, TGF-γ, IL-4), but not all markers (TNF-γ, IL-6, MMP-9), cytokines and other inflammation (98). In addition, lipoic acid supplementation did not reduce the severity of multiple sclerosis symptoms, as assessed by the Expanded Disability Status Scale (EDSS) scoring system (98, 99).

A two-year clinical trial designed to assess the effect of lipoic acid (1,200 mg/day) on loss of mobility and changes in brain volume in patients with progressive multiple sclerosis is ongoing (85).

Cognitive impairments and dementia

Studies in animal models of aging and neurodegenerative disease have indicated that lipoic acid administration might improve measures of spatial memory, learning capacity, and/or motor function (reviewed in 100).

It is not known whether oral lipoic acid supplementation can slow cognitive decline related to aging or pathological conditions in humans. An uncontrolled, open-label trial in nine patients with probable Alzheimer's disease and related dementias, who were also taking acetylcholinesterase inhibitors, reported that oral supplementation with 600 mg/day of lipoic acid appeared to stabilize cognitive function over a one-year period (101). A subsequent study that followed 43 patients for up to four years found those with mild dementia or moderate-early dementia who took lipoic acid (600 mg/day), in addition to acetylcholinesterase inhibitors, experienced slower cognitive decline compared to the typical cognitive decline of Alzheimer's patients as reported in the literature (102). However, the significance of these findings is difficult to assess without a control group for comparison. A randomized controlled trial found that oral supplementation with 1,200 mg/day of lipoic acid for 10 weeks was of no benefit in treating HIV-associated cognitive impairment (103). The results of another randomized trial in 39 patients with Alzheimer's disease suggested that supplementation with fish oil concentrate (high in omega-3 fatty acids) with or without lipoic acid (600 mg/day) for one year could delay the progression in cognitive and functional impairments assessed by the Instrumental Activities of Daily Living (IADL) scoring system compared to placebo (104). Interestingly, patients who took fish oil concentrate together with lipoic acid showed no worsening of global cognitive function (as assessed by the Mini-Mental State Examination [MMSE] score system) over 12 months as opposed to those who took either the fish oil concentrate alone or a placebo (104). Larger trials are needed to confirm these preliminary findings and further evaluate the usefulness of supplemental lipoic acid in the prevention and/or management of neurodegenerative diseases.

Weight management

A 2018 meta-analysis of randomized, placebo-controlled trials found that lipoic acid supplementation in those with high body mass index (BMI) resulted in significant, yet modest, reductions in weight (9 studies) and BMI (11 studies) in the absence of caloric restriction (except in one study) (105). Subgroup analyses revealed that weight loss was greater in overweight versus obese participants, in unhealthy versus healthy participants, with daily doses ≤600 mg, and for intervention period shorter than 10 weeks. There was no reduction in waist circumference with supplemental lipoic acid (5 studies) (105). Substantial weight and BMI reductions with lipoic acid supplementation in overweight or obese subjects were also reported in a prior meta-analysis (106).

Sources

Endogenous biosynthesis

R-lipoic acid is synthesized endogenously by humans (see Metabolism and Bioavailability).

Food sources

R-lipoic acid occurs naturally in food covalently bound to lysine in proteins (lipoyllysine; see **Figure 1**). Although lipoic acid is found in a wide variety of foods from plant and animal sources, quantitative information on the lipoic acid or lipoyllysine content of food is limited; published databases are lacking. Animal tissues with high lipoyllysine content (~1-3 µg/g dry wt) include kidney, heart, and liver, while lipoyllysine-rich vegetables include spinach and broccoli (107). Somewhat lower amounts of lipoyllysine (~0.5 µg/g dry wt) have been measured in tomatoes, peas, and Brussels sprouts.

Supplements

Unlike lipoic acid in foods, lipoic acid in supplements is not bound to protein. Moreover, the amounts of lipoic acid available in dietary supplements (50-600 mg) are likely as much as 1,000 times greater than the amounts that could be obtained from the diet. In Germany, lipoic acid is approved for the treatment of diabetic neuropathies and is available by prescription (108). Lipoic acid is available as a dietary supplement without a prescription in the US. Most lipoic acid supplements contain a racemic mixture of *R*-lipoic acid and *S*-lipoic acid (sometimes noted *d,l*-lipoic acid). Supplements that claim to contain only *R*-lipoic acid are usually more expensive, and information regarding their purity is not publicly available (109). Since taking lipoic acid with a meal decreases its bioavailability, it is generally recommended that lipoic acid be taken 30 min prior to a meal (see also Metabolism and Bioavailability) (8).

***Racemic mixture versus R*-lipoic acid only**

R-lipoic acid is the isomer that is synthesized by plants and animals and functions as a cofactor for mitochondrial enzymes in its protein-bound form (see Biological Activities). Direct comparisons of the bioavailability of the oral racemic mixture and *R*-lipoic acid supplements have not been published. Following the ingestion of *R,S*-lipoic acid, peak plasma concentrations of *R*-lipoic acid were found to be 40%-50% higher than *S*-lipoic acid, suggesting better absorption of *R*-lipoic acid. Both isomers were nonetheless rapidly metabolized and eliminated (6, 8, 11). In rats, *R*-lipoic acid was more effective than *S*-lipoic acid in enhancing insulin-stimulated glucose transport and metabolism in skeletal muscle (110), and *R*-lipoic acid was more effective than *R,S*-lipoic acid and *S*-lipoic acid in preventing cataracts (111). However, all of the published human studies have used *R,S*-lipoic acid (racemic mixture). It has been suggested that the presence of *S*-lipoic acid in the racemic mixture may limit the polymerization of *R*-lipoic acid and enhance its bioavailability (52). At present, it remains unclear which supplemental form is best to use in clinical trials.

Safety

Adverse effects

In general, high-dose lipoic acid administration has been found to have few serious side effects. Intravenous administration of lipoic acid at doses of 600 mg/day for three weeks (112) and oral lipoic acid at doses as high as 1,800 mg/day for six months (113) and 1,200 mg/day for two years (76) did not result in serious adverse effects when used to treat diabetic peripheral neuropathy. There was no significant difference in the incidence of adverse events and serious adverse events in patients with diabetic neuropathy who took 600 mg/day of lipoic acid for four years compared to those in the placebo group (78). Oral intake of 2,400 mg/day for two weeks was also found to be safe in a pilot study that included participants with multiple sclerosis (95). Two mild anaphylactoid reactions and one severe anaphylactic reaction, including laryngospasm, were reported after intravenous lipoic acid administration (55). The most frequently reported side effects of oral lipoic acid supplementation are allergic reactions affecting the skin, including rashes, hives, and itching. Abdominal pain, nausea, vomiting, diarrhea, and vertigo have also been reported, and one trial found that the incidence of nausea, vomiting, and vertigo was dose-dependent (77). Further, malodorous urine has been noted by people taking 1,200 mg/day of lipoic acid orally (95).

Pregnancy and lactation

A retrospective observational study reported that daily oral supplementation with 600 mg of lipoic acid (racemic mixture) during pregnancy and without interruption from a period spanning between week 10 and week 30 of gestation and until the end of week 37 was not associated with any adverse effect in mothers and their newborns (114). In absence of further evidence, lipoic acid supplementation during pregnancy should only be considered under strict medical supervision. The safety of lipoic acid supplements in lactating women has not been established and should thus be discouraged (115).

Children

A case of intoxication was reported in a 20-month old child (10.5 kg bw) after the accidental ingestion of four 600-mg tablets of lipoic acid (116). The child was admitted to hospital with seizure, acidosis, and unconsciousness. Symptomatic management and rapid elimination of lipoic acid led to a full recovery without sequelae within five days. The non-accidental ingestion of a very high dose of lipoic acid led to multi-organ failure and subsequent death of an adolescent girl (117).

Drug interactions

In theory, because lipoic acid supplementation may improve insulin-mediated glucose utilization (see Diabetes mellitus), there is a potential risk of hypoglycemia in diabetic patients using insulin or oral anti-diabetic agents (118). Consequently, blood glucose concentrations should be monitored closely when lipoic acid supplementation is added to diabetes treatment regimens. Yet, one study in 24 healthy volunteers reported no significant drug interactions with the co-administration of a single oral dose of lipoic acid (600 mg) and the oral anti-diabetic agents, glyburide (also called glybenclamide) or acarbose (Precose/Prandase/Glucobay) (119).

Nutrient interactions

Biotin

The chemical structure of biotin is similar to that of lipoic acid, and there is some evidence that high concentrations of lipoic acid can compete with biotin for transport across cell membranes (120, 121). The administration of high doses of lipoic acid by injection to rats decreased the activity of two biotin-dependent enzymes by about 30%-35% (122), but it is not known whether oral or intravenous lipoic acid supplementation substantially increases the requirement for biotin in humans (123).

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Phytochemicals

Phytochemicals can be defined, in the strictest sense, as chemicals produced by plants. However, the term is generally used to describe chemicals from plants that may affect health, but are not essential nutrients. While there is ample evidence to support the health benefits of diets rich in fruit, vegetables, legumes, whole grains, and nuts, evidence that these effects are due to specific nutrients or phytochemicals is limited. Because plant-based foods are complex mixtures of bioactive compounds, information on the potential health effects of individual phytochemicals is linked to information on the health effects of foods that contain those phytochemicals.

Select a phytochemical from the list for more information.

The information on dietary phytochemicals from the Linus Pauling Institute's Micronutrient Information Center is now available in a book titled, *An Evidence-based Approach to Phytochemicals and Other Dietary Factors*. The book can be purchased from the Linus Pauling Institute or Thieme Medical Publishers.

- Carotenoids
- Chlorophyll and Chlorophyllin
- Curcumin
- Fiber
- Flavonoids
- Garlic
- Indole-3-Carbinol
- Isothiocyanates
- Lignans
- Phytosterols
- Resveratrol
- Soy Isoflavones

Carotenoids

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α-Carotene, β-Carotene, β-Cryptoxanthin, Lycopene, Lutein, and Zeaxanthin

日本語

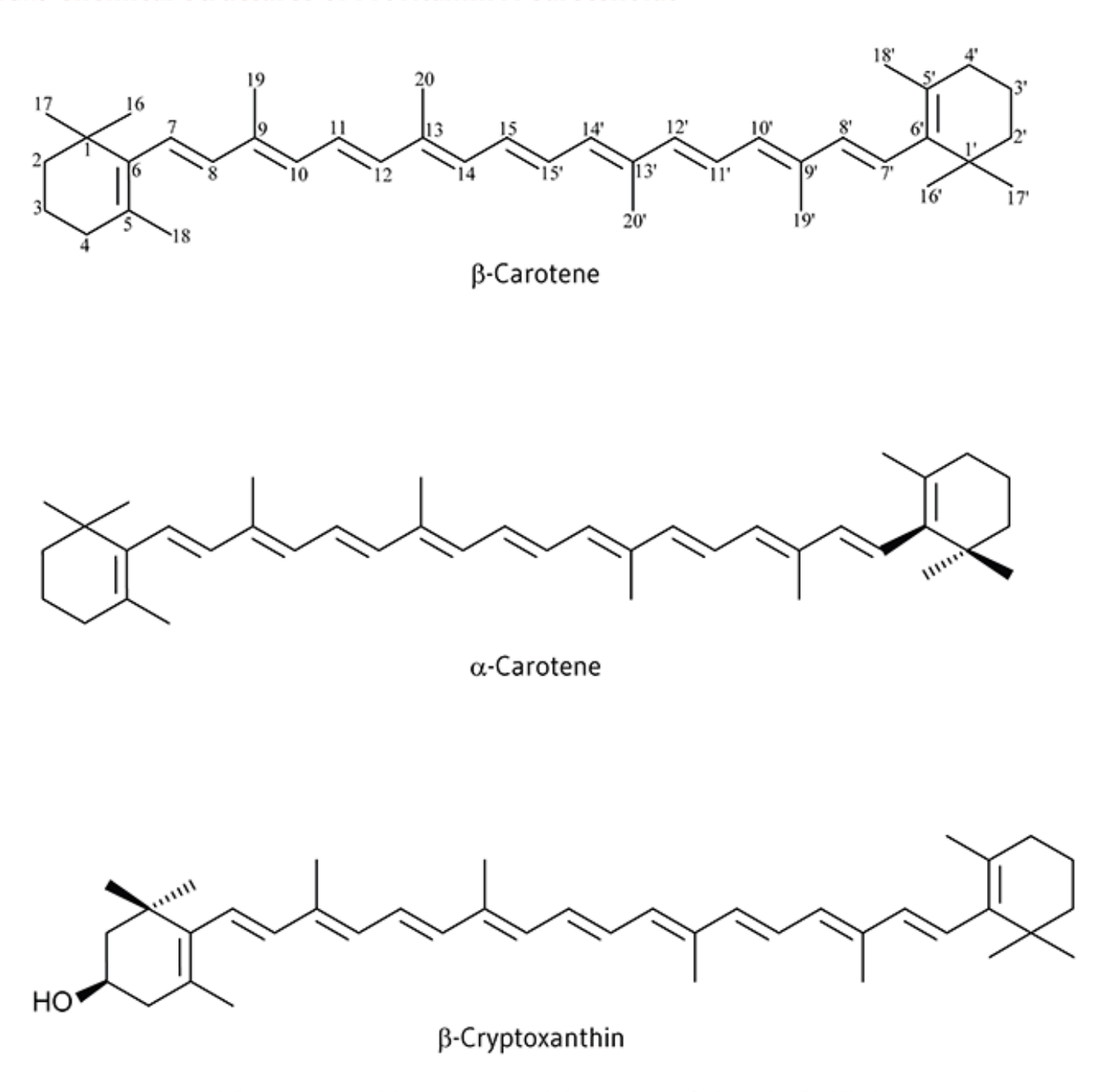
Summary

- Carotenoids are yellow, orange, and red pigments synthesized by plants. The most common carotenoids in North American diets are α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene. *(More information)*
- Provitamin A carotenoids, α-carotene, β-carotene, and β-cryptoxanthin, can be converted by the body to retinol (vitamin A). In contrast, no vitamin A activity can be derived from lutein, zeaxanthin, and lycopene. *(More information)*
- Dietary lutein and zeaxanthin are selectively taken up into the macula of the eye, where they absorb up to 90% of blue light and help maintain optimal visual function. *(More information)*
- At present, it is unclear whether the biological effects of carotenoids in humans are related to their antioxidant activity and/or other non-antioxidant activities. *(More information)*
- Although the results of observational studies suggest that diets high in carotenoid-rich fruit and vegetables are associated with reduced risks of cardiovascular disease and some cancers, high-dose β-carotene supplements did not reduce the risk of cardiovascular disease or cancer in large randomized controlled trials. *(More information)*
- Two randomized controlled trials found that high-dose β-carotene supplements increased the risk of lung cancer in smokers and former asbestos workers. *(More information)*
- Recent meta-analyses of observational studies reported an inverse association between blood lycopene concentration and risk of developing prostate cancer. To date, most small-scale intervention studies found little-to-no benefit of lycopene supplements in reducing incidence or severity of prostate cancer in high-risk patients. *(More information)*
- Observational studies have suggested that diets rich in lutein and zeaxanthin may help slow the development of age-related macular degeneration (AMD). Randomized controlled trials found that lutein and zeaxanthin supplements could improve visual acuity and slow the progression to advanced AMD in subjects with AMD. *(More information)*
- Evidence is lacking to suggest a role for lutein and zeaxanthin in the management of other eye conditions, including cataracts, diabetic retinopathy, and retinopathy of maturity. *(More information)*
- Carotenoids are best absorbed with fat in a meal. Chopping, puréeing, and cooking carotenoid-containing vegetables in oil generally increase the bioavailability of the carotenoids they contain. *(More information)*

Introduction

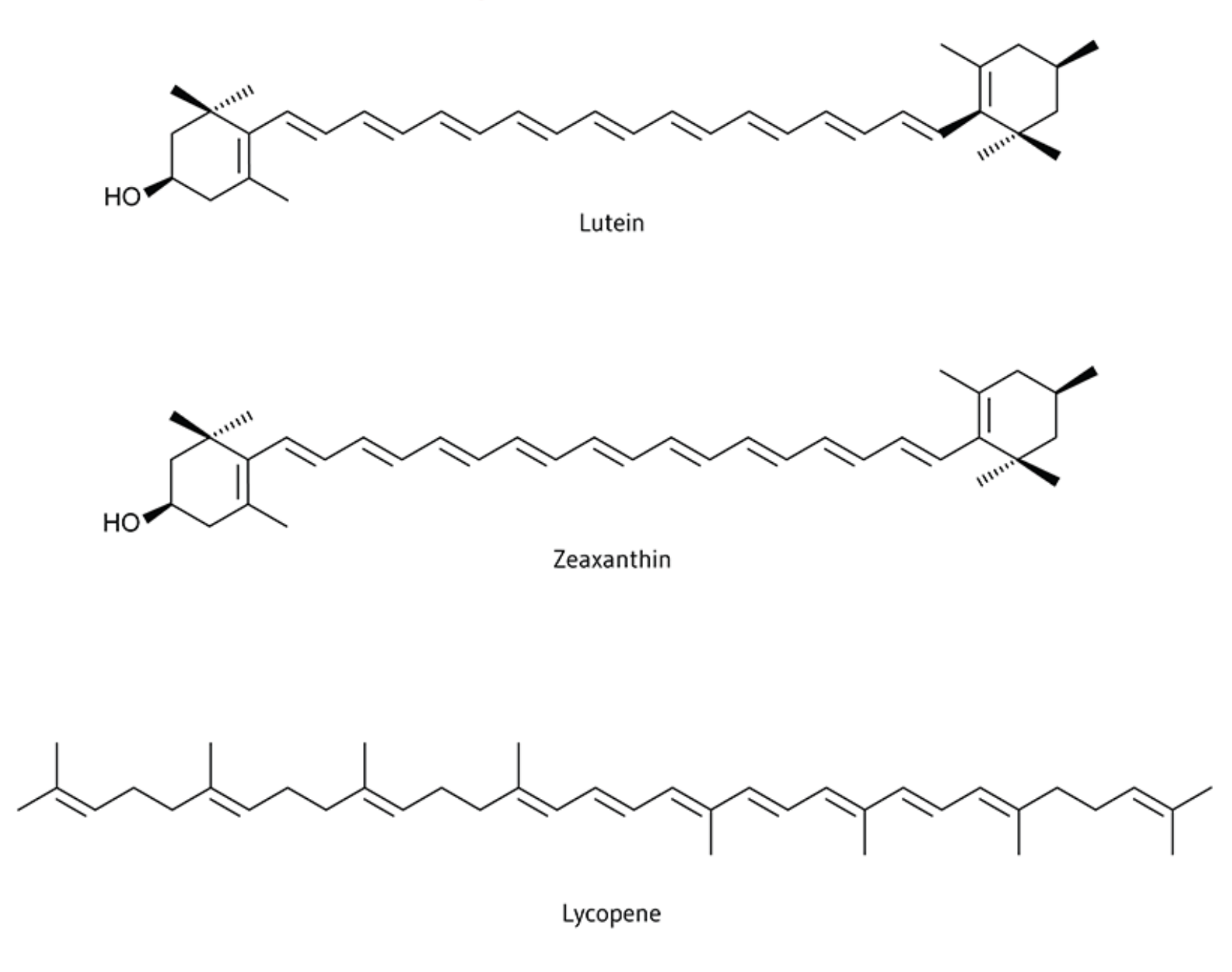
Carotenoids are a class of more than 750 naturally occurring pigments synthesized by plants, algae, and photosynthetic bacteria (1). These richly colored molecules are the sources of the yellow, orange, and red colors of many plants. Fruit and vegetables provide most of the 40 to 50 carotenoids found in the human diet. α-Carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene are the most common dietary carotenoids (1). α-Carotene, β-carotene and β-cryptoxanthin are provitamin A carotenoids, meaning they can be converted by the body to retinol (**Figure 1**). Lutein, zeaxanthin, and lycopene are nonprovitamin A carotenoids because they cannot be converted to retinol (**Figure 2**).

Figure 1. *All-trans* Chemical Structures of Provitamin A Carotenoids



β-Carotene, α-carotene, and β-cryptoxanthin are potential sources of vitamin A. All three carotenoids have a long carbon chain terminated at each end by a ionone ring. Carotenoids with oxygen added to ionone rings like β-cryptoxanthin are known as xanthophyll carotenoids. Other xanthophylls commonly found in the human diet are non-provitamin A lutein and zeaxanthin.

Figure 2. *All-trans* Chemical Structures of Nonprovitamin A Carotenoids



Absorption, Metabolism, and Bioavailability

For dietary carotenoids to be absorbed intestinally, they must be released from the food matrix and incorporated into mixed micelles (mixtures of bile salts and several types of lipids). Food processing and cooking help release carotenoids embedded in their food matrix and increase intestinal absorption (1). Moreover, carotenoid absorption requires the presence of fat in a meal. As little as 3 to 5 g of fat in a meal appears sufficient to ensure carotenoid absorption (2, 3), although the minimum amount of dietary fat required may be different for each carotenoid. The type of fat (e.g., medium-chain vs. long-chain triglycerides), the presence of soluble fiber, and the type and amount of carotenoids (e.g., esterified vs. non-esterified) in the food also appear to influence the rate and extent of carotenoid absorption (reviewed in 4). Because they do not need to be released from the plant matrix, carotenoid supplements (in oil) are more efficiently absorbed than carotenoids in food (3). Although carotenoids were initially thought to be absorbed within the cells that line the intestine (enterocytes) only by passive diffusion, recent investigations identified the apical membrane transporters, Scavenger Receptor-class B type I (SR-BI) and Cluster Determinant 36 (CD36), suggesting active uptake of carotenoids as well (5).

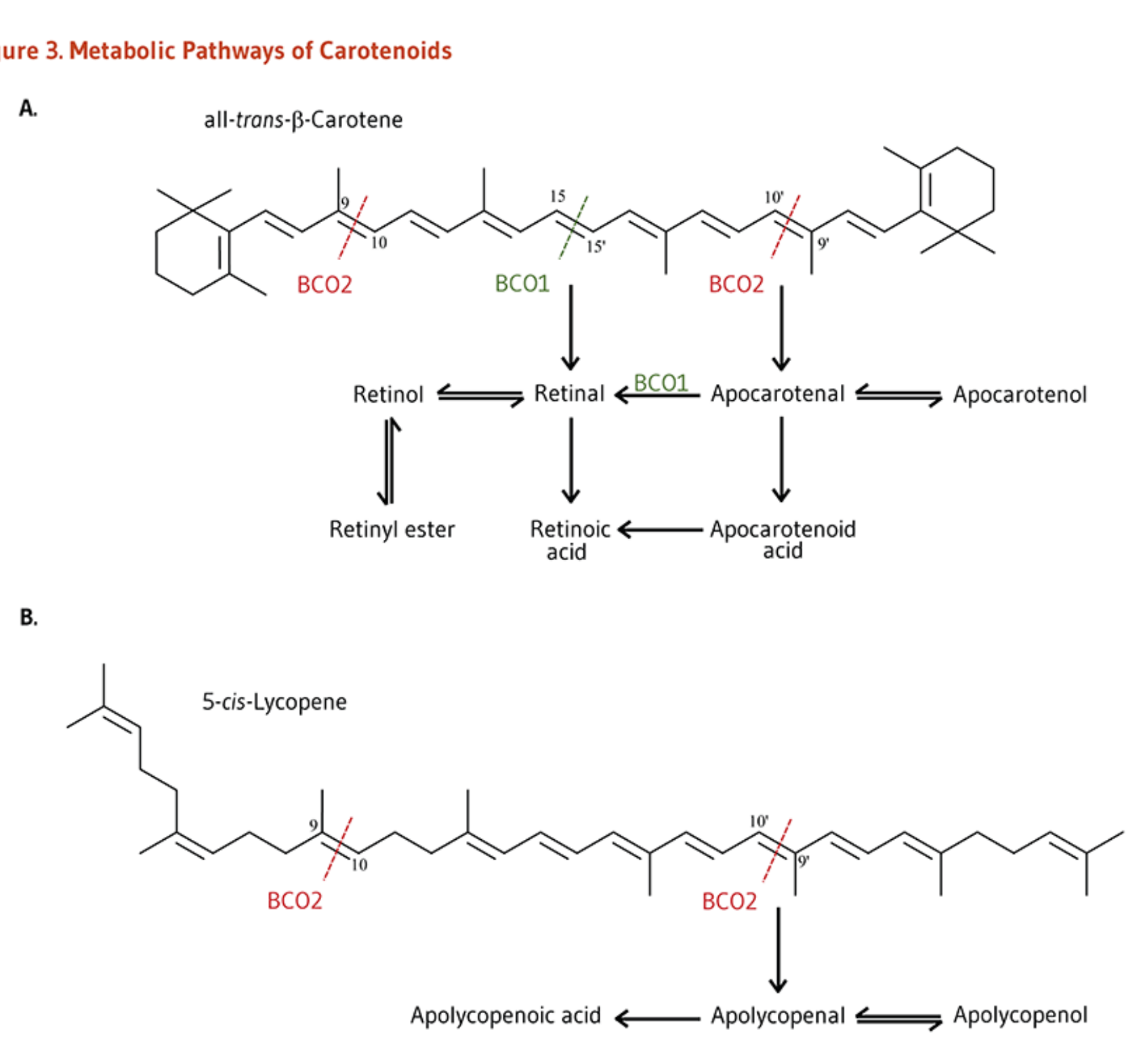
Within the enterocytes, provitamin A carotenoids may be cleaved by either β-carotene 15,15'-oxygenase 1 (BCO1) or by β-carotene 9',10'-oxygenase 2 (BCO2) (**Figure 3**). BCO1 catalyzes the cleavage of provitamin A carotenoids into retinal, which is further reduced to retinol (vitamin A) or oxidized to retinoic acid (the biologically active form of vitamin A). β-Apocarotenal derived from the cleavage of β-carotene by BCO2 can be cleaved further by BCO1 to produce retinal. Although provitamin A carotenoids can be converted into apocarotenals by BCO2, the activity of this enzyme is higher toward nonprovitamin A carotenoids. Conversely, BCO1 shows limited affinity toward nonprovitamin A carotenoids (1).

Within the enterocytes, uncleaved carotenoids and retinyl esters (derived from retinol) are incorporated into triglyceride-rich lipoproteins called chylomicrons, secreted into lymphatic vessels, and then released in the bloodstream (1). Triglycerides are depleted from circulating chylomicrons through the activity of an enzyme called lipoprotein lipase, resulting in the formation of chylomicron remnants. Chylomicron remnants are taken up by the liver, where carotenoids can be cleaved by BCO1/BCO2 or incorporated into lipoproteins and secreted back into the circulation for delivery to extrahepatic tissues. Of note, more hydrophilic molecules in the enterocytes like retinoic acid and apocarotenals can be transported directly to the liver through the portal blood system.

The conversion of provitamin A carotenoids to retinol is influenced by the vitamin A status of the individual (6). The regulatory mechanism involving the intestine-specific homeobox (ISX) transcription factor can block carotenoid uptake and vitamin A production by inhibiting the expression of SR-BI and BCO1. ISX is under the control of retinoid acid and retinoic acid receptor (RAR)-dependent mechanisms such that, when vitamin A stores are high, ISX is activated and both provitamin A carotenoid absorption and conversion to retinol are inhibited. Conversely, during vitamin A insufficiency, the expression of both SR-BI and BCO1 is no longer repressed by ISX, allowing for provitamin A carotenoid absorption and conversion to retinol (1).

Interindividual variations in blood and tissue concentrations of carotenoids have been attributed to genetic differences among individuals. Specifically, a number of single nucleotide polymorphisms (SNPs) — corresponding to changes of one nucleotide in the sequence of genes — have been identified in genes coding for proteins involved in intestinal uptake, transport, and metabolism of carotenoids (7). Specifically, SNPs within genes coding for SR-BI, CD36, and BCO1 are suspected to affect the expression and/or activity of these proteins and, in turn, individual carotenoid status (7).

Figure 3. Metabolic Pathways of Carotenoids



A. BCO1 catalyzes the symmetrical cleavage of provitamin A carotenoids like β-carotene at the 15, 15' double bond to produce one or two molecules of retinal. Retinal can be oxidized to retinoic acid or reduced to retinol, and further converted to retinyl ester for storage or transport. Provitamin A carotenoids may also be cleaved by BCO2 at either the 9,10 or 9',10' double bond, giving rise to apocarotenals. The latter can be converted to apocarotenols or apocarotenoid acids. Apocarotenals and apocarotenoid acids can be converted to retinals and retinoic acids.

B. Nonprovitamin A carotenoids, lutein and zeaxanthin, can be cleaved by BCO2 at either the 9,10 or 9',10' double bond to produce apocarotenals (not shown here). The cleavage of *cis*-lycopene by BCO2 at either the 9,10 or 9',10' double bond produces apolycopenal, which may be oxidized to apolycopenoic acid or reduced to apolycopenol.
BCO1, β-carotene 15,15'-oxygenase 1; BCO2, β-carotene 9',10'-oxygenase 2.

Biological Activities

Provitamin A function

Vitamin A is essential for normal growth and development, immune system function, and vision (see the article on Vitamin A). Currently, the only essential function of carotenoids recognized in humans is that of the provitamin A carotenoids, α-carotene, β-carotene, and β-cryptoxanthin, to serve as a source of vitamin A (8).

Retinol activity equivalents (RAEs)

Provitamin A carotenoids are less easily absorbed than preformed vitamin A and must be converted to retinol and other retinoids by the body (**Figure 3**). The efficiency of conversion of provitamin A carotenoids into retinol is highly variable, depending on factors like food matrix, food preparation, and one's digestive and absorptive capacities (9).

The most recent international standard of measure for vitamin A is retinol activity equivalent (RAE), which represents vitamin A activity as retinol. It has been determined that 2 micrograms (μg) of β-carotene in oil provided as a supplement could be converted by the body to 1 μg of retinol, giving it an RAE ratio of 2:1. However, 12 μg of β-carotene from food are required to provide the body with 1 μg of retinol, giving dietary β-carotene an RAE ratio of 12:1. Other provitamin A carotenoids in food are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1. RAE ratios are shown in **Table 1**.

Table 1. Retinol Activity Equivalent (RAE) Ratios for Preformed Vitamin A and Provitamin A Carotenoids

Quantity Consumed	Quantity Bioconverted to Retinol	RAE Ratio
1 μg of dietary or supplemental preformed vitamin A	1 μg of retinol	1:1
2 μg of supplemental β-carotene	1 μg of retinol	2:1
12 μg of dietary β-carotene	1 μg of retinol	12:1
24 μg of dietary α-carotene	1 μg of retinol	24:1
24 μg of dietary β-cryptoxanthin	1 μg of retinol	24:1

Antioxidant activity

In plants, carotenoids have the important antioxidant function of quenching (deactivating) singlet oxygen, an oxidant formed during photosynthesis (10). Test tube studies indicated that lycopene is one of the most effective quenchers of singlet oxygen among carotenoids (11). They also suggested that carotenoids could inhibit the oxidation of fats (i.e., lipid peroxidation) under certain conditions, but their actions in humans appear to be more complex (12). Although important for plants, the relevance of singlet oxygen quenching to human health is less clear (1).

Nrf2-dependent antioxidant pathway

Some evidence suggests that carotenoids and/or their metabolites may upregulate the expression of antioxidant and detoxifying enzymes via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway (reviewed in 13). Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol. Keap1 responds to oxidative stress signals by freeing Nrf2. Upon release, Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE) located in the promoter of genes coding for antioxidant/detoxifying enzymes and scavengers. Nrf2/ARE-dependent genes code for numerous mediators of the antioxidant response, including glutamate-cysteine ligase (GCL), glutathione S-transferases (GSTs), thioredoxin, NAD(P)H quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) (14). A recent study showed an increase in the level of the major antioxidant glutathione and a protection against TNFα-induced oxidative stress in retinal pigment epithelial cells (RPE) following lycopene-mediated Nrf2 activation and GCL induction (15). Nrf2 activation by lycopene also protected RPE against TNFα-mediated proinflammatory signaling involving nuclear factor-κB (NF-κB) activation and intercellular adhesion molecule-1 (ICAM-1) expression (15). Lycopene was shown to trigger Nrf2-mediated antioxidant pathway in various cell types (16-18). At present, evidence from animal and human studies is very limited (13).

Blue light filtering

The long system of alternating double and single bonds common to all carotenoids allows them to absorb light in the visible range of the spectrum (10). This feature has particular relevance to the eye, where lutein, zeaxanthin, and meso-zeaxanthin (derived from lutein) efficiently absorb blue light. Depending on the carotenoid pigment density at the center of the eye's retina (macula), up to 90% of blue light can be absorbed by these pigments. Reducing the amount of short-wavelength light that reaches the critical visual structures of the eye may protect them from light-induced oxidative damage (19). Because the only source of these plant pigments in the eye is diet, a number of observational and intervention studies have examined the potential of dietary and supplemental lutein and zeaxanthin to protect against age-related eye diseases (see Age-related macular degeneration and Cataracts). Supplemental lutein, alone or with zeaxanthin, was found to improve contrast sensitivity and protect against visual fatigue in young and/or healthy individuals (20-23). Lutein has also been suggested to improve visual function through stimulating neuronal signaling efficiency in the eye (24).

Intercellular communication

Carotenoids can facilitate communication between neighboring cells grown in culture by stimulating the synthesis of connexin proteins (25). Connexins form pores (gap junctions) in cell membranes, allowing cells to communicate through the exchange of small molecules. This type of intercellular communication is important for maintaining cells in a differentiated state and is often lost in cancer cells. Carotenoids facilitate intercellular communication by increasing the expression of the gene encoding a connexin protein, an effect that appears unrelated to the vitamin A or antioxidant activities of various carotenoids (26) and involving a retinoic acid receptor (RAR)-independent mechanism (27).

Immune function

Because vitamin A is essential for normal immune system function, it is difficult to determine whether the effects of provitamin A carotenoids are related to their vitamin A activity or other activities of carotenoids. Although some clinical trials have found that β-carotene supplementation improves several biomarkers of immune function (28-30), increasing intakes of lycopene and lutein — carotenoids without vitamin A activity — have not resulted in similar improvements in biomarkers of immune function (31-33).

Deficiency

Although consumption of provitamin A carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) can prevent vitamin A deficiency (see the article on Vitamin A), no overt deficiency symptoms have been identified in people consuming low-carotenoid diets if they consume adequate vitamin A (8). After reviewing the published scientific research in 2000, the Food and Nutrition Board of the Institute of Medicine concluded that the existing evidence was insufficient to establish a recommended dietary allowance (RDA) or adequate intake (AI) for carotenoids. The Board has set an RDA for vitamin A (see the article on Vitamin A). Recommendations by the National Cancer Institute, American Cancer Society, and American Heart Association to consume a variety of fruit and vegetables daily are aimed, in part, at increasing intakes of carotenoids.

Disease Prevention

Cancer

Lung cancer

Dietary carotenoids: Several large prospective cohort studies, including the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), have examined potential associations between carotenoid intake and/or blood concentrations and lung cancer (36). In a meta-analysis of eight prospective cohort studies, including NHS and HPFS, the highest versus lowest quantile of total carotenoid intake was significantly associated with a 21% reduced risk of lung cancer. For the individual carotenoids, the risk of lung cancer was estimated to be 20% and 14% lower with the highest versus lowest intakes of β-cryptoxanthin and lycopene, respectively. In contrast, dietary intakes of β-carotene, α-carotene, and lutein/zeaxanthin were not found to be significantly linked to a reduced risk of developing lung cancer (36). In addition, an analysis of the pooled results of 11 nested case-control and four prospective cohort studies found no association between serum concentrations of total carotenoids, β-carotene, α-lycopene, β-cryptoxanthin, and lutein/zeaxanthin and lung cancer. Only high versus low serum lycopene concentrations could be linked to a 29% lower risk of lung cancer (36). Any protective effect of dietary carotenoids against the development of lung cancer is likely small and not statistically significant (36).

Supplemental β-carotene: The effect of β-carotene supplementation on the risk of developing lung cancer has been examined in three large randomized, placebo-controlled trials. In Finland, the A-Tocopherol Beta-Carotene (ATBC) cancer prevention trial evaluated the effects of 20 mg/day of β-carotene and/or 50 mg/day of α-tocopherol on more than 29,000 male smokers (37), and in the United States, the β-Carotene And Retinol Efficacy Trial (CARET) evaluated the effects of a combination of 30 mg/day of β-carotene and 25,000 IU/day of retinol (preformed vitamin A) in 18,314 men and women who were smokers, former smokers, or had a history of occupational asbestos exposure (38). Unexpectedly, the risk of lung cancer in the groups taking β-carotene supplements was increased by 16% after six years in the ATBC participants and by 28% after four years in the CARET participants. In contrast, the Physicians' Health Study (PHS) examined the effect of β-carotene supplementation (50 mg every other day) on cancer risk in 22,071 male physicians in the United States, of whom only 11% were current smokers (39). In that lower risk population, β-carotene supplementation for more than 12 years was not associated with an increased risk of lung cancer. In addition, in the Linxian General Population trial conducted in about 29,000 Chinese participants, randomization to 15 mg/day of β-carotene, 30 mg/day of α-tocopherol, and 15 μg/day of selenium, was not found to be associated with lung cancer mortality 10 years after the intervention ended (40).

Although the reasons for the increase in lung cancer risk are not yet clear and several mechanisms have been proposed (41). The US Preventive Services Task Force estimated that the risks of high-dose β-carotene supplementation outweigh any potential benefits for cancer prevention and recommended against supplementation, especially in smokers or other high-risk populations (42).

Prostate cancer

Prostate cancer is the most common cancer affecting US men, more prevalent than lung and colorectal cancers (34).

Dietary lycopene: Several early prospective cohort studies have suggested that lycopene-rich diets were associated with significant reductions in the risk of prostate cancer, particularly more aggressive forms (43). However, pooled data analyses of observational studies that examined potential links between dietary intakes and/or circulating concentrations of lycopene and risk of prostate cancer have given mixed results. An early meta-analysis that combined the results of 10 case-control and four prospective studies found that men with the highest intakes of raw tomatoes, cooked tomatoes, or dietary lycopene had a 11 to 19% lower risk of prostate cancer (44). In addition, pooled data from two case-control and five nested case-control studies showed a 26% lower risk of prostate cancer in participants with the highest serum concentrations of lycopene (44). Most recently, a meta-analysis of observational studies found no association of prostate cancer risk with dietary lycopene intakes (10 case-cohort and two prospective cohort studies) but an inverse association with blood lycopene concentrations (two case-control, nine nested case-control, and one cohort studies) (45, 46). Additionally, a meta-analysis of 15 nested case-control studies conducted by the Endogenous Hormones, Nutritional Biomarkers, and Prostate Cancer Collaborative Group showed an inverse association between circulating lycopene concentrations and risk of advanced stage and/or aggressive prostate cancer, while no association was found with risk of non-aggressive or localized disease (47).

While there is considerable scientific interest in the potential for lycopene to help prevent prostate cancer, it is not yet clear whether the prostate cancer risk reduction observed in some observational studies is related to lycopene itself, other compounds in tomatoes, or other factors associated with lycopene-rich diets (48). Of note, the 2014 World Cancer Research Fund International report on *Diet, Nutrition, Physical Activity, and Prostate Cancer* suggested the need for better designed studies to establish whether consumption of lycopene-containing foods could be linked to a lower risk of prostate cancer (49).

Supplemental lycopene: To date, a few short-term, dietary intervention studies using lycopene in patients with precancerous prostate lesions (high grade prostatic intraepithelial neoplasia; HGPIN) or prostate cancer have been completed. Specifically, two small randomized controlled studies have recently examined the effect of lycopene supplementation for up to six months in men with HGPIN (50, 51). The consumption of 30 to 35 mg/day of supplemental lycopene in the form of tomato extract (50), or together with selenium (55 mg/day) and green tea catechins (600 mg/day) (51), showed no benefit on the rate of progression to prostate cancer at six-month (50, 51) and 37-month follow-ups (51). Earlier small trials in men with HGPIN led to similar conclusions (reviewed in 52). Additionally, a randomized controlled trial in men with localized prostate cancer found that supplementation with 15, 30, or 45 mg of lycopene (until prostatectomy) did not significantly increase plasma lycopene concentration, modify the ratio of steroid hormones in blood, or reduce the concentration of markers of proliferation (i.e., prostate-specific antigen [PSA] and Ki-67) compared to placebo (53). In another trial, 54 patients with metastatic prostate cancer were randomized to orchidectomy alone or orchidectomy plus 4 mg/day of lycopene (54). The proportion of complete clinical response to treatment — assessed by serum PSA and/or bone scan returning to normal — and patient survival rate were found to be significantly higher in patients supplemented with lycopene (54).

Large-scale, controlled clinical trials are needed to further examine the safety and efficacy of long-term use of lycopene supplements for prostate cancer prevention or treatment.

Other types of cancer

In a meta-analysis of 12 prospective cohort studies, no association was found between total and individual carotenoid intake and risk of breast cancer, except with β-carotene for which a 5% reduction in breast cancer risk was estimated for every 5 mg/day increment in consumption (55). In a pooled analysis of 14 nested case-control studies and one follow-up study of a clinical trial, reductions in breast cancer risk were found to be associated with blood concentrations of total carotenoids (-26%), α-carotene (-20%), and lutein (-30%) (55). Another study that recalibrated data for consistency across eight large prospective cohorts before pooled analysis found reduced breast cancer risk to be associated with the highest versus lowest quintile of blood concentrations of total carotenoids (-21%), β-carotene (-17%), and lycopene (-22%) (56). Further analyses found an inverse association between the blood concentrations of β-carotene and α-carotene and risk of estrogen receptor-negative (ER-), but not estrogen receptor-positive (ER+), breast tumors (56). A similar result was recently reported in a case-control study nested within the multicenter, large, European Prospective Investigation into Cancer and Nutrition (EPIC) study (57).

Another case-control study nested within the EPIC study found a 31% lower risk of colorectal cancer with the highest versus lowest quartile of β-carotene intake, while no associations were shown with blood concentrations of other carotenoids or total carotenoids (58). The nested case-control study was included in a recent meta-analysis of 22 observational studies that failed to find associations between carotenoid intakes and colorectal cancer (59).

Pooled data from mostly case-control studies also suggested that higher intakes of individual carotenoids, especially β-cryptoxanthin and lycopene, might be associated with a reduced risk of cancers of the mouth, pharynx, and larynx (60). However, the results of case-control studies are more likely to be distorted by bias than results of prospective studies.

Examining blood concentrations of each carotenoid in relation to cancer subsites may help overcome limitations associated with dietary data and differences in carotenoid absorption.

Eye diseases

Age-related macular degeneration

In Western countries, degeneration of the macula, the center of the eye's retina, is a leading cause of blindness in older adults. Long-term blue light exposure and oxidative damage in the outer segments of photoreceptors may lead to drusen and/or pigment abnormalities in the macula, increasing the risk of age-related macular degeneration (AMD) and central blindness.

Dietary lutein and zeaxanthin: The carotenoids found in the retina are lutein and zeaxanthin, which are both of dietary origin, and meso-zeaxanthin, which is derived from lutein. These three carotenoids are present in high concentrations in the macula (known as macular pigment), where they are efficient absorbers of blue light. They may prevent a substantial amount of the blue light entering the eye from reaching the underlying structures involved in vision and protect against light-induced oxidative damage, which is thought to play a role in the pathology of age-related macular degeneration (reviewed in 19). It is also possible, though not proven, that lutein, zeaxanthin, and meso-zeaxanthin, act directly to neutralize oxidants formed in the retina.

Increasing dietary consumption of lutein and zeaxanthin was shown to raise their serum concentration and macular pigment density (61, 62). Some, but not all, observational studies have provided evidence that higher intakes of lutein and zeaxanthin are associated with lower risk of age-related macular degeneration (AMD) (63). While cross-sectional and retrospective case-control studies found that higher levels of lutein and zeaxanthin in the diet (64-66), blood (67, 68), and retina (69, 70) were associated with a lower incidence of AMD, several prospective cohort studies found no relationship between baseline dietary intakes or serum concentrations of lutein and zeaxanthin and the risk of developing AMD over time (71-74). A recent report examined the association between the incidence of AMD and calculated dietary intakes and predicted plasma concentrations of lutein and zeaxanthin in older adults (≥50 years) from two large prospective cohorts, the Nurses' Health Study (NHS; 63,443 women) and the Health Professionals Follow-up Study (HPFS; 38,603 men), followed for 26 years and 24 years, respectively (75). The highest versus lowest quintile of predicted plasma lutein and zeaxanthin scores was associated with a 41% lower risk of advanced AMD, yet no association was found with intermediate AMD. The evidence also suggested that the consumption of about 6 mg/day of lutein and zeaxanthin from fruit and vegetables (compared with less than 2 mg/day) may decrease the risk of advanced AMD (75).

Supplemental lutein and zeaxanthin: The first randomized controlled trial in patients with atrophic AMD found that supplementation with 10 mg/day of lutein slightly improved visual acuity after one year compared to a placebo (76). The effects of long-term lutein supplementation on atrophic AMD were further investigated in combination with antioxidant vitamins and minerals in the Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-blind, placebo-controlled trial. In AREDS, oral supplementation with β-carotene (15 mg/day), vitamin C (500 mg/day), vitamin E (400 IU/day), zinc (80 mg/day as zinc oxide), and copper (2 mg/day as cupric oxide) for five years was shown to reduce the risk of developing advanced AMD by 25% (77). In the AREDS2 study conducted in 4,203 participants at risk for developing late AMD, supplemental lutein (10 mg/day) and zeaxanthin (2 mg/day), in combination with β-carotene, vitamin C, vitamin E, zinc, and copper (the 'AREDS' formulation), did not slow the progression to advanced AMD, although subgroup analyses revealed a benefit in those with the lowest dietary intakes of lutein + zeaxanthin (77). A total of 3,036 subjects were further randomized to various combinations of carotenoids; supplementation with lutein and zeaxanthin significantly reduced the risk of progression to late AMD and to neovascular AMD compared to supplementation with β-carotene (78).

Several smaller (n=30-433) randomized controlled trials also suggested that supplementation with xanthophyll carotenoids would be beneficial in the management of AMD (reviewed in 79). A meta-analysis of eight trials that examined the effect of supplemental lutein (6 to 20 mg/day) or/and zeaxanthin (0 to 10 mg/day) in 1,176 AMD subjects for up to 36 months found improvements in visual acuity and contrast sensitivity with increased levels of xanthophyll carotenoids (80). Finally, a recent randomized, placebo-controlled trial found daily consumption of a buttermilk drink with egg yolks enriched with lutein (1.4 mg), zeaxanthin (0.2 mg), and an omega-3 polyunsaturated fatty acid (DHA; 160 mg) for one year improved visual acuity and macular pigment optical density in subjects with drusen and/or retinal pigment abnormalities (about half of them being classified as having early AMD) (81).

Supplemental β-carotene: The first randomized controlled trial designed to examine the effect of a carotenoid supplement on AMD used β-carotene in combination with vitamin C, vitamin E, and zinc because lutein and zeaxanthin were not commercially available as supplements at the time the trial began (82). Although the combination of antioxidants and zinc lowered the risk of developing advanced macular degeneration in individuals with signs of moderate-to-severe macular degeneration in at least one eye, it is unlikely that the benefit was related to β-carotene since it is not present in the retina. Supplementation of male smokers in Finland with 20 mg/day of β-carotene for six years did not decrease the risk of AMD compared to placebo (83). A placebo-controlled trial in a cohort of 22,071 healthy US men found that β-carotene supplementation (50 mg every other day) had no effect on the incidence of age-related maculopathy — an early stage of AMD (84). Recent systematic reviews of randomized controlled trials have concluded that there is no evidence that β-carotene supplementation prevents or delays the onset of AMD (85, 86).

Other retinopathies

Retinopathy of prematurity

Preterm infants have an immature retinal vascular system that places them at risk of developing retinopathy of prematurity (ROP). Basically, preterm birth halts the normal development of retinal vascular system, which results in a retina that is poorly vascularized and highly susceptible to hyperoxia. In order to meet metabolic demand, the hypoxic retina induces the production of proangiogenic factors like VEGF (vascular endothelial growth factor). These factors stimulate the development of new blood vessels (angiogenesis), causing aberrant vessels sprouting from the retina into the vitreous. It is thought that an imbalance between the production of reactive oxygen species (ROS) and the reduced levels of antioxidants in preterm infants contributes to ROP pathogenesis and causes additional damage to the retina (reviewed in 87).

Supplemental lutein and zeaxanthin: A randomized controlled trial in 62 preterm infants (≤32 weeks of gestational age) failed to observe any benefits regarding ROP incidence and severity with lutein (0.5 mg/kg/day) and zeaxanthin (0.02 mg/kg/day) supplemented from the seventh day post birth until about 10 weeks of age (88). In two other multicenter, placebo-controlled trials in a total of 343 preterm infants, a daily oral dose of 0.14 mg of lutein and 0.006 mg of zeaxanthin administered from the first week after birth did not significantly reduce ROP incidence or the rate of progression from early to more advanced stages of ROP occurrence (89, 90). A fourth multicenter, randomized controlled trial in 203 preterm infants found that administration of a formula containing carotenoids (lutein/zeaxanthin, lycopene, and β-carotene) had no effect on ROP incidence but limited the progression to severe ROP stages in infants with mild ROP compared to a carotenoid-free formula (91). Compared with the control formula, preterm infants free of ROP fed the carotenoid-containing formula had significantly increased plasma carotenoid concentrations, which were correlated with greater rod photoreceptor sensitivity (91). More research is needed to examine whether carotenoid supplementation might promote normal photoreceptor development and prevent ROP in preterm infants.

Diabetic retinopathy

Supplementation with lutein and zeaxanthin has been shown to help preserve retina integrity in diabetic rodents by reducing oxidative stress and inflammatory mediators (87). A higher ratio of plasma nonprovitamin A carotenoids (lutein, zeaxanthin, and lycopene) to vitamin A carotenoids (β-carotene, β-carotene, β-cryptoxanthin) was associated with a reduced risk of diabetic retinopathy in a cross-sectional analysis in 111 individuals with type 2 diabetes mellitus (92). Recent data from 1,430 individuals participating in the Atherosclerosis Risk In Communities (ARIC) study found no association between lutein intake and diabetic retinopathy after adjustment for confounding variables (93). To date, the role of carotenoids in the prevention of diabetic retinopathy has not been examined in clinical studies.

Cataracts

The primary function of the eye's lens is to collect and focus light on the retina. Ultraviolet light and oxidants can damage proteins in the lens, causing structural changes that result in the formation of opacities known as cataracts. As people age, cumulative damage to lens proteins often results in cataracts that are large enough to interfere with vision (10). Risk factors other than aging and sunlight exposure include smoking, diabetes mellitus, higher body mass index, and use of estrogen replacement therapy. An estimated 50 million US adults are projected to be affected by age-related cataracts by 2050 (94).

Dietary lutein and zeaxanthin: The observation that lutein and zeaxanthin are the only carotenoids in the human lens has stimulated interest in the potential for increased intakes of lutein and zeaxanthin to prevent or slow the progression of cataracts (reviewed in 79). Large prospective cohort studies have found that men and women with the highest intakes of foods rich in lutein and zeaxanthin, particularly spinach, kale, and broccoli, were 18%-50% less likely to require cataract extraction (95, 96) or develop cataracts (97-99). Moreover, plasma concentrations of lutein and zeaxanthin have been found to be inversely associated to the progression of nuclear cataract. Additional research is required to determine whether these findings are related specifically to lutein and zeaxanthin intake or to other factors associated with diets high in carotenoid-rich foods (63).

Supplemental lutein and zeaxanthin: The Age-related Eye Disease Study 2 (AREDS2) failed to show an effect of supplemental lutein (10 mg/day) and zeaxanthin (2 mg/day; supplementation for a median of 4.7 years) on the risk of developing cataract, on the progression to severe cataract or to cataract surgery, and on visual acuity (100). However, the results might have been confounded by the fact that most participants were better nourished than the general population and/or used multivitamins that have been found to decrease the risk of developing cataract (101). Additional limitations to consider in interpreting the results have been reviewed elsewhere (100). Additional interventions are required to study whether supplemental lutein and zeaxanthin might be helpful in the prevention of cataract.

Supplemental β-carotene: Evidence from observational studies that cataracts were less prevalent in people with high dietary intakes and blood concentrations of carotenoids led to the inclusion of β-carotene supplements in several large randomized controlled trials of antioxidants. The results of those trials have been somewhat conflicting. β-Carotene supplementation (20 mg/day) for more than six years did not affect the prevalence of cataracts or the frequency of cataract surgery in male smokers living in Finland (83). In contrast, a 12-year study of male physicians in the US found that β-carotene supplementation (50 mg every other day) decreased the risk of cataracts in smokers but not in nonsmokers (102). Note that use of β-carotene supplements have been shown to increase the risk of lung cancer in smokers (see Supplemental β-carotene in lung cancer). Three randomized controlled trials examined the effect of an antioxidant combination that included β-carotene, vitamin C, and vitamin E on the progression of cataracts. Two trials found no benefit after supplementation for five years (103) or more than six years (104), but one trial found a small decrease in the progression of cataracts after three years of supplementation (105). Overall, the results of randomized controlled trials suggest that the benefit of β-carotene supplementation in slowing the progression of age-related cataracts does not outweigh the potential risks.

Cardiovascular disease

Dietary carotenoids: Because carotenoids are very soluble in fat and very insoluble in water, they circulate in lipoproteins, along with cholesterol and other fats. Evidence that low-density lipoprotein (LDL) oxidation plays a role in the development of atherosclerosis led scientists to investigate the role of antioxidant compounds like carotenoids in the prevention of cardiovascular disease (106). The thickness of the inner layers of the carotid arteries can be measured noninvasively using ultrasound technology. This measurement of carotid intima-media thickness is considered a reliable marker of atherosclerosis (107). A number of case-control and cross-sectional studies have found higher blood concentrations of carotenoids to be associated with significantly lower measures of carotid artery intima-media thickness (108-113). Additionally, higher plasma carotenoids at baseline have been associated with significant reductions in risk of cardiovascular disease in some prospective cohort studies (114-118) but not in others (119-122).

More recently, an analysis of data from the 2003-2006 US National Health And Nutrition Examination Survey (NHANES) in a sample of 2,856 adults found that serum total carotenoid concentration was inversely associated to blood concentrations of two cardiovascular risk factors, C-reactive protein (CRP) and total homocysteine (123). HDL-cholesterol concentration was found to be positively associated with α-carotene, β-cryptoxanthin, and lutein/zeaxanthin concentrations, but only the latter was inversely associated with LDL-cholesterol (123). Finally, a recent meta-analysis of observational studies reported lower risks of coronary heart disease (-12%) and stroke (-18%) in individuals in the highest versus lowest tertile of blood lutein concentration (124).

While the results of several prospective studies indicate that people with higher intakes of carotenoid-rich fruit and vegetables are at lower risk of cardiovascular disease (122, 125-127), it is not yet clear whether this effect is a result of carotenoids or other factors associated with diets high in carotenoid-rich fruit and vegetables.

Supplemental β-carotene: In contrast to the results of observational studies suggesting that high dietary intakes of carotenoid-rich fruit and vegetables may decrease cardiovascular disease risk, four randomized controlled trials found no evidence that β-carotene supplements in doses ranging from 20 to 50 mg/day were effective in preventing cardiovascular disease (39, 128-130). Based on the results of these randomized controlled trials, the US Preventive Health Services Task Force found good evidence to suggest that β-carotene supplements provided no benefit in the prevention of cardiovascular disease in healthy adults (42). Thus, although diets rich in β-carotene have generally been associated with reduced cardiovascular disease risk in observational studies, there is no evidence that β-carotene supplementation reduces cardiovascular disease risk (131).

Osteoporosis

A recent experimental study found that the administration of β-cryptoxanthin to ovariectomized mice limited bone resorption by inhibiting osteoclast differentiation but had no effect on osteoblast-driven bone formation (132). Yet, evidence of a protective role of β-cryptoxanthin — and other individual carotenoids — against bone loss in humans is scarce. In the prospective Framingham Osteoporosis Study, data analysis of 603 participants found no association between β-cryptoxanthin intake and changes in bone mineral density (BMD) over a four-year period (133). In contrast, intakes of total and individual carotenoids (β-carotene, lycopene, and lutein/zeaxanthin) were positively associated with proximal femur BMD in men over a four-year period, while lycopene intake was positively linked to lumbar spine BMD in women (133). The 17-year follow-up of participants in the Framingham Osteoporosis Study (946 participants) showed those in the highest tertile of total carotenoid intake (median intake: 23.7 mg/day) had a 51% lower risk of hip fracture compared to those in the lowest tertile (median intake: 7.3 mg/day) (134). In a much larger prospective study — the Singapore Chinese Health Study — in 63,257 men and women followed for 10 years, the highest versus lowest quartile of total carotenoid intake was associated with a 37% lower risk of hip fracture in men but not in women (135). Dietary intakes of α- and β-carotene — but not of β-cryptoxanthin, lycopene, and lutein/zeaxanthin — were inversely associated with hip fracture risk in men (135). Nevertheless, in a small, four-year, Japanese prospective cohort study in 457 adults, the risk of osteoporosis was 93% lower in postmenopausal women in the highest versus lowest tertile of serum β-cryptoxanthin concentration (136). No such association was reported with serum concentrations of other individual carotenoids. Whether carotenoid supplementation may help prevent bone loss and reduce the risk of osteoporosis in older individuals is currently unknown.

Cognitive function

Observational studies have suggested that dietary lutein may be of benefit in maintaining cognitive health (137, 138). As stated above, among the carotenoids, lutein and its isomer zeaxanthin are the only two that cross the blood-retina barrier to form macular pigment in the eye. Lutein also preferentially accumulates in the brain (139, 140). Recent studies suggested that lutein and zeaxanthin concentrations in the macula were correlated with brain lutein and zeaxanthin status and might be used as a biomarker to assess cognitive health (140-142). Additionally, in the Georgia Centenarian Study, the analysis of cross-sectional data from 47 centenarian decedents showed a positive association between post-mortem measures of brain lutein concentrations and pre-mortem measures of cognitive function (139). Brain lutein concentrations were found to be significantly lower in individuals with mild cognitive impairment compared to those with normal cognitive function (139). In a small, four-month, double-blind, placebo-controlled study in older women (ages, 60 to 80 years) without cognitive impairment, supplementation with lutein (12 mg/day) and zeaxanthin (~0.5 mg/day) significantly improved cognitive test performance (143). Nevertheless, the Age-related Eye Disease Study 2 (AREDS2) failed to show an effect of supplemental lutein (10 mg/day) and zeaxanthin (2 mg/day; supplementation for a median of 4.7 years) on the cognitive test scores of 3,741 participants (mean age, 72.7 years) (144).

Sources

Food sources

The most prevalent carotenoids in the human diet are α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin (8). Most carotenoids in foods are found in the *all-trans* form (see **Figure 1** and **Figure 2** above), although cooking may result in the formation of other isomers. The relatively low bioavailability of carotenoids from most foods compared to supplements is partly due to the fact that they are associated with proteins in the plant matrix (145). Chopping, homogenizing, and cooking disrupt the plant matrix, increasing the bioavailability of carotenoids (3). For example, the bioavailability of lycopene from tomatoes is substantially improved by heating tomatoes in oil (146, 147).

α-Carotene and β-carotene

α-Carotene and β-carotene are provitamin A carotenoids, meaning they can be converted in the body to vitamin A. The vitamin A activity of β-carotene in food is $^1/_{12}$ that of retinol (preformed vitamin A). Thus, it would take 12 μg of β-carotene from food to provide the equivalent of 1 μg (0.001 mg) of retinol. The vitamin A activity of α-carotene from foods is $^1/_{24}$ that of retinol, so it would take 24 μg of α-carotene from food to provide the equivalent of 1 μg of retinol. Orange and yellow vegetables like carrots and winter squash are rich sources of α- and β-carotene. Spinach is also a rich source of β-carotene, although the chlorophyll in spinach leaves hides the yellow-orange pigment. Some foods that are good sources of α-carotene and β-carotene are listed in **Table 2** and **Table 3** (148).

Table 2. α-Carotene Content of Selected Foods

Food	Serving	α-Carotene (mg)
Pumpkin, canned	1 cup	11.7
Carrot juice, canned	1 cup (8 fl oz)	10.2
Carrots, cooked	1 cup	5.9
Carrots, raw	1 medium	2.1
Mixed vegetables, frozen, cooked	1 cup	1.8
Winter squash, baked	1 cup	1.4
Plantains, raw	1 medium	0.8
Collards, frozen, cooked	1 cup	0.2
Tomatoes, raw	1 medium	0.1
Tangerines, raw	1 medium	0.09
Peas, edible-podded, frozen, cooked	1 cup	0.09

Table 3. β-Carotene Content of Selected Foods

Food	Serving	β-Carotene (mg)
Carrot juice, canned	1 cup (8 fl oz)	22.0
Pumpkin, canned	1 cup	17.0
Spinach, frozen, cooked	1 cup	13.8
Sweet potato, baked	1 medium	13.1
Carrots, cooked	1 cup	13.0
Collards, frozen, cooked	1 cup	11.6
Kale, frozen, cooked	1 cup	11.5
Turnip greens, frozen, cooked	1 cup	10.6
Pumpkin pie	1 piece	7.4
Winter squash, cooked	1 cup	5.7
Carrots, raw	1 medium	5.1
Dandelion greens, cooked	1 cup	4.1
Cantaloupe, raw	1 cup	3.2

β-Cryptoxanthin

Like α- and β-carotene, β-cryptoxanthin is a provitamin A carotenoid. The vitamin A activity of β-cryptoxanthin from food was estimated to be $^1/_{24}$ that of retinol, so it would take 24 μg of β-cryptoxanthin from food to provide the equivalent of 1 μg of retinol. Orange and red fruit and vegetables like sweet red peppers and oranges are particularly rich sources of β-cryptoxanthin. Some foods that are good sources of β-cryptoxanthin are listed in **Table 4** (148).

Table 4. β-Cryptoxanthin Content of Selected Foods

Food	Serving	β-Cryptoxanthin (mg)
Pumpkin, cooked	1 cup	3.6
Papayas, raw	1 medium	2.3
Sweet red peppers, cooked	1 cup	0.6
Sweet red peppers, raw	1 medium	0.6
Orange juice, fresh	1 cup (8 fl oz)	0.4
Tangerines, raw	1 medium	0.4
Carrots, frozen, cooked	1 cup	0.3

Yellow corn, frozen, cooked	1 cup	0.2
Watermelon, raw	1 wedge (1/16 of a melon that is 15 inches long x 7.5 inches in diameter)	0.2
Paprika, dried	1 teaspoon	0.2
Oranges, raw	1 medium	0.2
Nectarines, raw	1 medium	0.1

Lycopene

Lycopene gives tomatoes, pink grapefruit, watermelon, and guava their red color. It has been estimated that 80% of the lycopene in the US diet comes from tomatoes and tomato products like tomato sauce, tomato paste, and ketchup (catsup) (149). Lycopene is not a provitamin A carotenoid because it cannot be converted to retinol. Some foods that are good sources of lycopene are listed in **Table 5** (148).

Table 5. Lycopene Content of Selected Foods

Food	Serving	Lycopene (mg)
Tomato paste, canned	1 cup	75.4
Tomato purée, canned	1 cup	54.4
Tomato soup, canned, condensed	1 cup	26.4
Vegetable juice cocktail, canned	1 cup	23.3
Tomato juice, canned	1 cup	22.0
Watermelon, raw	1 wedge (1/16 of a melon that is 15 inches long x 7.5 inches in diameter)	13.0
Tomatoes, raw	1 cup	4.6
Ketchup (catsup)	1 tablespoon	2.5
Pink grapefruit, raw	½ grapefruit	1.7
Baked beans, canned	1 cup	1.3

Lutein and zeaxanthin

Although lutein and zeaxanthin are different compounds, they are both classified as xanthophylls and nonprovitamin A carotenoids (see **Figure 2** above). Some methods used to quantify lutein and zeaxanthin in food do not separate the two compounds, so they are typically reported as lutein and zeaxanthin or lutein + zeaxanthin. Both pigments are present in a variety of fruit and vegetables. Dark green leafy vegetables like spinach and kale are particularly rich sources of lutein but poor sources of zeaxanthin (150). Although relatively low in lutein, egg yolks and avocados are highly bioavailable sources of lutein. Good sources of dietary zeaxanthin include yellow corn, orange pepper, orange juice, honeydew (melon), and mango (150). Some foods containing lutein and zeaxanthin are listed in **Table 6** (148).

Table 6. Lutein + Zeaxanthin Content of Selected Foods

Food	Serving	Lutein + Zeaxanthin (mg)
Spinach, frozen, cooked	1 cup	29.8
Kale, frozen, cooked	1 cup	25.6
Turnip greens, frozen, cooked	1 cup	19.5
Collards, frozen, cooked	1 cup	18.5
Dandelion greens, cooked	1 cup	9.6
Mustard greens, cooked	1 cup	8.3
Summer squash, cooked	1 cup	4.0
Peas, frozen, cooked	1 cup	3.8
Winter squash, baked	1 cup	2.9
Pumpkin, cooked	1 cup	2.5
Brussel sprouts, frozen, cooked	1 cup	2.4
Broccoli, frozen, cooked	1 cup	2.0
Sweet yellow corn, boiled	1 cup	1.5
Avocado, raw	1 medium	0.4
Egg yolk, raw	1 large	0.2

For more information on the carotenoid content of certain foods, search USDA's FoodData Central database.

Supplements

Dietary supplements providing purified carotenoids and combinations of carotenoids are commercially available in the US without a prescription. Carotenoids are best absorbed when taken with a meal containing fat.

α-Carotene

Supplements containing a mixture of carotenoids may include α-carotene. As a provitamin A carotenoid, supplemental α-carotene can contribute to fulfill vitamin A requirements. It is not known whether the relative bioavailability of supplemental α-carotene is greater than that of dietary α-carotene.

α-Cryptoxanthin

Supplements containing a mixture of carotenoids may include α-cryptoxanthin. As a provitamin A carotenoid, supplemental α-cryptoxanthin can contribute to fulfill vitamin A requirements. It is not known whether the relative bioavailability of supplemental α-cryptoxanthin is greater than that of dietary α-cryptoxanthin.

β-Carotene

β-Carotene is sold as individual supplements and also found in supplements marketed to promote visual health (151). Commercially available β-carotene supplements usually contain between 1.5 mg and 15 mg of either synthetic β-carotene or natural β-carotene (mainly from the algae *Dunaliella salina*) per softgel capsule (150). As a provitamin A carotenoid, β-carotene may be used to provide all or part of the vitamin A in multivitamin supplements. The provitamin A activity of β-carotene from supplements is much higher than that of β-carotene from food: it takes only 2 micrograms [μg] (0.002 mg) of β-carotene from supplements to provide 1 μg of retinol (preformed vitamin A) compared to 12 μg of dietary β-carotene.

Of note, the β-carotene content of supplements is often listed in international units (IU) rather than μg: 3,000 μg (3 mg) of supplemental β-carotene provides 5,000 IU of vitamin A.

Lycopene

Lycopene has no provitamin A activity. Synthetic lycopene and lycopene from natural sources, mainly tomatoes, are available as nutritional supplements containing up to 15 mg of lycopene per softgel capsule (150).

Lutein and zeaxanthin

Lutein and zeaxanthin are not provitamin A carotenoids. Lutein and zeaxanthin supplements are available as free carotenoids (non-esterified) or as esters (esterified to fatty acids). Both forms appear to have comparable bioavailability (152). Many commercially available lutein and zeaxanthin supplements have much higher amounts of lutein than zeaxanthin (150). Supplements containing only lutein or zeaxanthin are also available.

Safety

Toxicity

β-Carotene

Although β-carotene can be converted to vitamin A, the conversion of β-carotene to vitamin A decreases when body stores of vitamin A are high (see Absorption, Metabolism, and Bioavailability). This may explain why high doses of β-carotene have never been found to cause vitamin A toxicity. High doses of β-carotene (up to 180 mg/day) have been used to treat erythropoietic protoporphyria, a photosensitivity disorder, without toxic side effects (8).

Lycopene, lutein, and zeaxanthin

No toxicities have been reported (153).

Adverse effects

β-Carotene

Increased lung cancer risk: Two randomized controlled trials in smokers and former asbestos workers found that supplementation with 20 to 30 mg/day of β-carotene for 4 to 6 years was associated with significant 16%-28% increases in the risk of lung cancer compared to placebo (see Supplemental β-carotene in lung cancer). Although the reasons for these findings are not yet clear, the potential risk of lung cancer in smokers and other high-risk groups supplemented with high-dose β-carotene outweigh any possible benefits for chronic disease prevention (42). It should be noted that there is no evidence that β-carotene supplementation may harm nonsmokers.

Carotenodermia: High doses of β-carotene supplements (≥30 mg/day) and the consumption of large amounts of carotene-rich food have resulted in a yellow discoloration of the skin (xanthoderma) known as carotenodermia. Carotenodermia is not associated with any underlying health problems and resolves when supplementation with β-carotene is discontinued or dietary carotene intake is reduced.

Lycopene

Lycopenodermia: High intakes of lycopene-rich food or supplements may result in a deep orange discoloration of the skin known as lycopenodermia. Because lycopene is more intensely colored than the carotenes, lycopenodermia may occur at lower doses than carotenodermia (8).

Lutein and zeaxanthin

Adverse effects of lutein and zeaxanthin have not been reported (150).

Safety in pregnancy and lactation

β-Carotene

Unlike vitamin A, high doses of β-carotene taken by pregnant women have not been associated with increased risk of birth defects (8). However, the safety of high-dose β-carotene supplements in pregnancy and lactation has not been well studied. Although there is no reason to limit dietary β-carotene intake, pregnant and breast-feeding women should avoid consuming more than 3 mg/day (1,500 μg RAE/day; 5,000 IU/day) of β-carotene from supplements unless they prescribed under medical supervision.

Other carotenoids

The safety of carotenoid supplements other than β-carotene in pregnancy and lactation has not been established, so pregnant and breast-feeding women should obtain carotenoids from food rather than supplements. There is no reason to limit the consumption of carotenoid-rich fruit and vegetables during pregnancy (150).

Drug interactions

The cholesterol-lowering agents, cholestyramine (Questran) and colestipol (Colestid), can reduce absorption of fat-soluble vitamins and carotenoids, as can mineral oil and Orlistat (Xenical), a drug used to treat obesity (150). Colchicine, a drug used to treat gout, can cause intestinal malabsorption. However, long-term use of 1 to 2 mg/day of colchicine did not affect serum β-carotene concentrations in one study (154). Increasing gastric pH through the use of proton-pump inhibitors (Omeprazole, Lansoprazole) may decrease the absorption of a single dose of a β-carotene supplement, but the effect is unlikely to be clinically significant (155).

Antioxidant supplements and statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors)

A three-year randomized controlled trial in 160 patients with documented coronary heart disease (CHD) and low serum high density lipoprotein (HDL) concentrations found that a combination of simvastatin (Zocor) and niacin increased HDL2 levels, inhibited the progression of coronary artery stenosis, and decreased the frequency of cardiovascular events, including myocardial infarction and stroke (156). Surprisingly, when an antioxidant combination of 1,000 mg of vitamin C, 536 mg of *RRR*-α-tocopherol (vitamin E), 100 μg of selenium, and 25 mg of β-carotene daily was taken with the simvastatin-niacin combination, the protective effects were diminished. Since the antioxidants were taken together in this trial, the individual contribution of β-carotene cannot be determined. In contrast, a much larger randomized controlled trial of simvastatin and an antioxidant combination of 297 mg of *RRR*-α-tocopherol, 250 mg of vitamin C, and 20 mg of β-carotene daily in more than 20,000 men and women with CHD or diabetes mellitus found that the antioxidant combination did not diminish the cardioprotective effects of simvastatin therapy over a five-year period (157). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplements and cholesterol-lowering agents, such as niacin and statins.

Interactions with food

Fat substitute Olestra

In a controlled feeding study, consumption of 18 g/day of the fat substitute Olestra (sucrose polyester; Olean) resulted in a 27% decrease in serum carotenoid concentrations after three weeks (158). Studies in people before and after the introduction of Olestra-containing snacks to the marketplace found that total serum carotenoid concentrations decreased by 15% in those who reported consuming at least 2 g/day of Olestra (159). One study in adults found that those who consumed more than 4.4 g of Olestra weekly experienced a 9.7% decline in total serum carotenoids compared to those not consuming Olestra (160).

Plant sterol- or stanol-containing foods

Some studies found that the regular use of plant sterol-containing spreads resulted in modest, 10%-20% decreases in the plasma concentrations of some carotenoids, particularly α-carotene, β-carotene, and lycopene (see the article on Phytosterols) (161, 162). However, advising people who use plant sterol- or stanol-containing margarines to consume an extra serving of carotenoid-rich fruit or vegetables daily prevented decreases in plasma carotenoid concentrations (163, 164).

Alcohol

The relationships between alcohol consumption and carotenoid metabolism are not well understood. There is some evidence that regular alcohol consumption inhibits the conversion of β-carotene to retinol (165). Increases in lung cancer risk associated with high-dose β-carotene supplementation in two randomized controlled trials were enhanced in those with higher alcohol intakes (38, 166).

Interactions among carotenoids

The results of metabolic studies suggested that high doses of β-carotene competed with lutein and lycopene for absorption when consumed at the same time (167-169). However, the consumption of high-dose β-carotene supplements did not adversely affect serum carotenoid concentrations in long-term clinical trials (170-173).

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Chlorophyll and Metallo-Chlorophyll Derivatives

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Summary

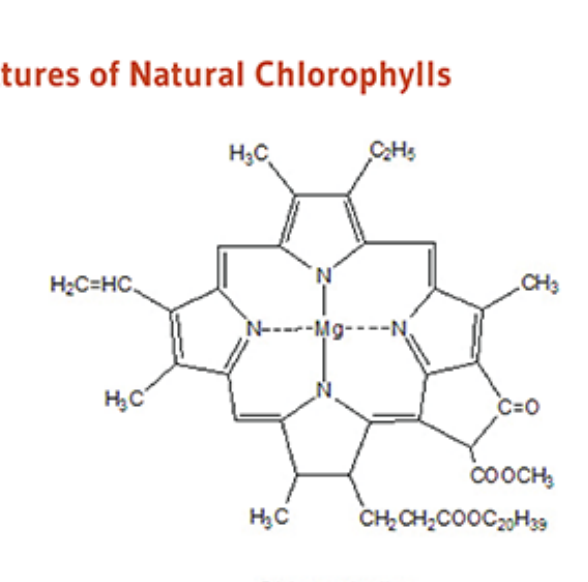
- Chlorophyll a and chlorophyll b are natural, fat-soluble chlorophylls found in plants. *(More information)*
- Sodium copper chlorophyllin (SCC) is a semi-synthetic mixture of water-soluble sodium copper salts derived from chlorophyll. *(More information)*
- SCC has been used orally as an internal deodorant and topically in the treatment of slow-healing wounds for more than 50 years without any serious side effects. *(More information)*
- Chlorophylls and SCC form tight molecular complexes with some chemicals known or suspected to cause cancer, and in doing so, may block carcinogenic effects. Carefully controlled studies have not been undertaken to determine whether a similar mechanism might limit uptake of required nutrients. *(More information)*
- Supplementation with SCC before meals substantially decreased a urinary biomarker of aflatoxin-induced DNA damage in a Chinese population at high risk of liver cancer due to unavoidable, dietary aflatoxin exposure from moldy grains and legumes. *(More information)*
- Scientists are hopeful that SCC supplementation will be helpful in decreasing the risk of liver cancer in high-risk populations with unavoidable, dietary aflatoxin exposure. However, it is not yet known whether SCC or natural chlorophylls will be useful in the prevention of cancers in people who are not exposed to significant levels of dietary aflatoxin. *(More information)*

Introduction

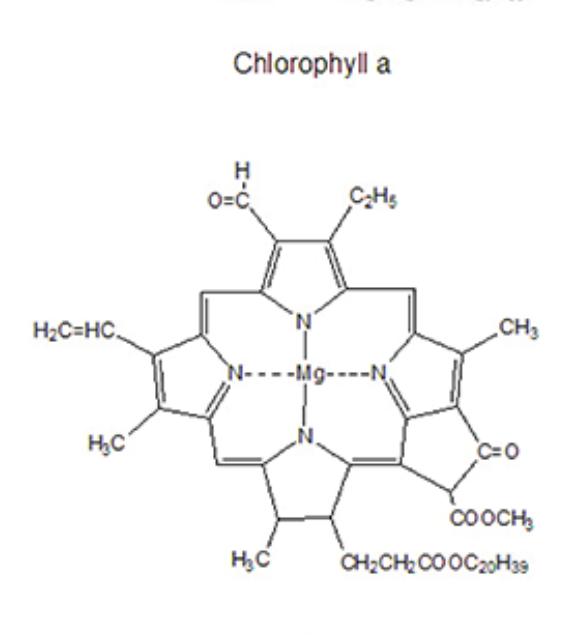
Chlorophyll is the pigment that gives plants and algae their green color. Plants use chlorophyll to trap light needed for photosynthesis (1). The basic structure of chlorophyll is a porphyrin ring similar to that of heme in hemoglobin, although the central atom in chlorophyll is magnesium instead of iron. The long hydrocarbon (phytol) tail attached to the porphyrin ring makes chlorophyll fat-soluble and insoluble in water. Chlorophyll a and chlorophyll b represent about 99% of the chlorophyll species found in edible plants (**Figure 1**; 2), while some algae and microalgae contain minor quantities of chlorophyll c pigments (e.g., *Laminaria ochroleuca*, *Undaria pinnatifida*) (3). Chlorophyll a and b only have a small difference in one of the side chains but an intact phytol tail, while the common characteristic of chlorophyll c isoforms is the absence of a phytol tail. These structural differences cause each type of chlorophyll to absorb light at slightly different wavelengths.

Metallo-chlorophyll derivatives, including chlorophyllins, can be chemically synthesized or produced in industrial food processing; these compounds contain zinc, iron, or copper in place of the central magnesium atom (2). The most studied chlorophyllin, sodium copper chlorophyllin (SCC), is a semi-synthetic mixture of sodium copper salts derived from chlorophyll (4, 5). SCC is often simply called 'chlorophyllin' in the older scientific literature, with newer publications specifying whether iron, zinc, copper, or magnesium chlorophyllin were studied. During its synthesis, the magnesium atom at the center of the ring is replaced with copper (or other metals), and the phytol tail is lost. Unlike natural chlorophyll, chlorophyllins (regardless of the metal used) are water-soluble. Although the content of different SCC mixtures may vary, two compounds commonly found in commercial SCC are trisodium copper chlorin e_6 and disodium copper chlorin e_4 (**Figure 2**).

Figure 1. Chemical Structures of Natural Chlorophylls

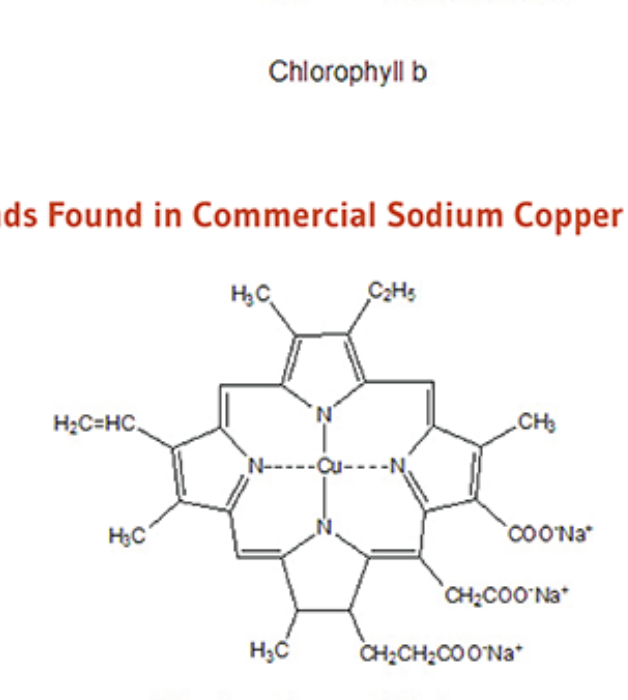


Chlorophyll a

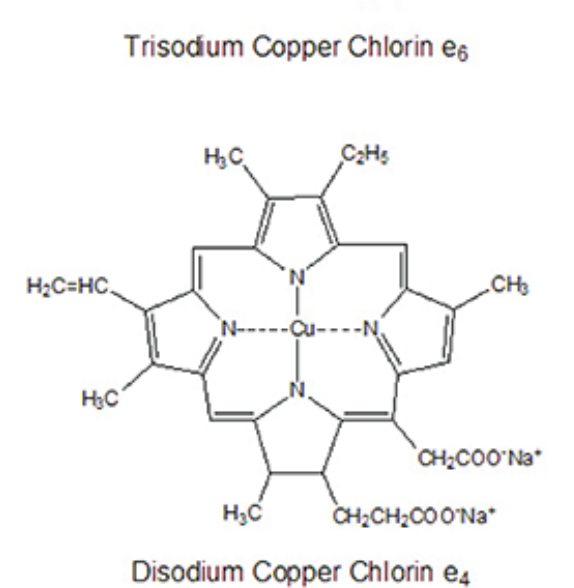


Chlorophyll b

Figure 2. Two Compounds Found in Commercial Sodium Copper Chlorophyllin



Trisodium Copper Chlorin e_6



Disodium Copper Chlorin e_4

Metabolism and Bioavailability

Little is known about the bioavailability and metabolism of chlorophyll in humans, although it is known that chlorophyll undergoes extensive metabolism once consumed. Animal model studies show only about 1%-3% of chlorophyll is absorbed, while the rest is excreted in the feces, primarily as pheopytin and pyropheophytin metabolites, indicating that significant transformation and microbial metabolism occur in the gastrointestinal tract (reviewed in 2). A recent study in eight healthy adults found pheophytin and pheophorbide derivatives in the blood of most subjects following consumption of 1.2 kg boiled spinach, a concentrated source of chlorophyll (6).

Sodium copper chlorophyllin was originally thought to be poorly absorbed because of its lack of apparent toxicity. However, a placebo-controlled clinical trial found that significant amounts of copper chlorin e$_4$ in the serum of people taking chlorophyllin tablets (300 mg/day) (7), indicating that it is indeed absorbed. *In vitro* studies have found chlorin e$_4$ to have a higher stability than chlorin e$_6$(2).

More research, however, is needed to understand the bioavailability and metabolism of natural chlorophylls and chlorin compounds in synthetic chlorophyllin.

Biological Activities

Complex formation with other molecules

Chlorophyll and sodium copper chlorophyllin are able to form tight molecular complexes with certain chemicals known or suspected to cause cancer, including polyaromatic hydrocarbons found in tobacco smoke (8), some heterocyclic amines found in cooked meat (9), and aflatoxin-B$_1$ (10). The binding of chlorophyll or SCC to these potential carcinogens may interfere with gastrointestinal absorption of potential carcinogens, reducing the amount that reaches susceptible tissues (11). This has been demonstrated in humans: a cross-over study in three volunteers that used accelerator mass spectrometry to study the pharmacokinetics of an ultra-low dose of aflatoxin-B$_1$ found a 150-mg dose of either SCC or chlorophyll could decrease absorption of aflatoxin-B$_1$ (12).

Antioxidant effects

SCC can neutralize several physically relevant oxidants *in vitro* (13-16), and limited data from animal studies suggest that SCC supplementation may decrease oxidative damage induced by chemical carcinogens and radiation (17, 18). While chlorophyll and its derivatives have demonstrated antioxidant activity in *in vitro* assays (15, 19), the relevance of these findings to humans is not clear.

Modification of the metabolism and detoxification of carcinogens

To initiate the development of cancer, some chemicals (procarcinogens) must first be metabolized to active carcinogens that are capable of damaging DNA or other critical molecules in susceptible tissues. Since enzymes in the cytochrome P450 family are required for the activation of some procarcinogens, inhibition of cytochrome P450 enzymes may decrease the risk of some types of chemically induced cancers. *In vitro* studies indicate that SCC may decrease the activity of cytochrome P450 enzymes (8, 20, 21). Phase II biotransformation enzymes promote the elimination of potentially harmful toxins and carcinogens from the body. Limited data from animal studies indicate that SCC may increase the activity of the phase II enzyme quinone reductase (22).

Therapeutic effects

One *in vitro* study showed that human colon cancer cells undergo cell cycle arrest after treatment with SCC (23). The mechanism involved inhibition of ribonucleotide reductase activity. Ribonucleotide reductase plays a pivotal role in DNA synthesis and repair and is a target of currently used cancer therapeutic agents, such as hydroxyurea (23). While this may provide a potential avenue for SCC in the clinical setting, sensitizing cancer cells to DNA damaging agents, *in vivo* studies are needed.

Metal absorption

The porphyrin structure of chlorophyll is analogous to the heme structure found in blood and muscle tissue. Because heme-bound iron has higher bioavailability than nonheme iron (the most common form of iron in plant-based sources, e.g., legumes, spinach), iron uptake from iron chlorophyll is of interest. Toxicity studies in rats suggest iron chlorophyllin is generally safe for mammalian consumption (24). *In vitro* studies demonstrate that iron chlorophyllin is as good as heme in delivering iron to intestinal cells, and significantly better than the most common supplemental form of iron (i.e., ferrous sulfate) when incorporated into most food matrices (25). However, work in this area is nascent and has not yet been validated in humans. It is also not known if metallo-chlorophyll derivatives of copper or zinc increase absorption of these essential divalent metals.

Disease Prevention

Aflatoxin-associated liver cancer

Aflatoxin-B$_1$ (AFB$_1$), a liver carcinogen produced by certain species of fungus, is found in moldy grains and legumes, including corn, peanuts, and soybeans (4, 11). In hot, humid regions of Africa and Asia with improper grain storage facilities, high levels of dietary AFB$_1$ are associated with increased risk of hepatocellular carcinoma. Moreover, the combination of hepatitis B infection and high dietary AFB$_1$ exposure increases the risk of hepatocellular carcinoma still further. In the liver, AFB$_1$ is metabolized to a carcinogen capable of binding DNA and causing mutations. In animal models of AFB$_1$-induced liver cancer, administration of SCC at the same time as dietary AFB$_1$ exposure significantly reduces AFB$_1$-induced DNA damage in the livers of rainbow trout and rats (26-28) and dose-dependently inhibits the development of liver cancer in trout (29). Likewise, natural chlorophyll has also been found to inhibit AFB$_1$-induced liver cancer in the rat (28). Collectively, this evidence supports a role for SCC and/or chlorophyll itself in limiting cancer initiation. In contrast, data suggest a limited role for SCC in influencing cancer progression. For example, one rat study found that SCC did not protect against aflatoxin-induced liver damage when given after tumor initiation (30).

Because of the long time period between AFB$_1$ exposure and the development of cancer in humans, an intervention trial might require as long as 20 years to determine whether SCC supplementation can reduce the incidence of hepatocellular carcinoma in people exposed to high levels of dietary AFB$_1$. However, a biomarker of AFB$_1$-induced DNA damage (AFB$_1$-N^7-guanine) can be measured in the urine, and high urinary levels of AFB$_1$-N^7-guanine have been associated with significantly increased risk of developing hepatocellular carcinoma (31). In order to determine whether chlorophyllin could decrease AFB$_1$-induced DNA damage in humans, a randomized, placebo-controlled intervention trial was conducted in 180 adults residing in a region in China where the risk of hepatocellular carcinoma is very high due to unavoidable, dietary AFB$_1$ exposure and a high prevalence of chronic hepatitis B infection (32). Participants took either 100 mg of SCC or a placebo before meals three times daily. After 16 weeks of treatment, urinary levels of AFB$_1$-N^7-guanine were 55% lower in those taking SCC than in those taking the placebo, suggesting that SCC supplementation before meals can substantially decrease AFB$_1$-induced DNA damage. Although a reduction in hepatocellular carcinoma has not yet been demonstrated in humans taking SCC, scientists are hopeful that supplementation will provide some protection to high-risk populations with unavoidable, dietary AFB$_1$ exposure (11).

It is not known whether SCC will be useful in the prevention of cancers in people who are not exposed to significant levels of dietary AFB$_1$, as is the case for most people living in the US. Many questions remain to be answered regarding the exact mechanisms of cancer prevention by SCC, the implications for the prevention of other types of cancer, and the potential for natural chlorophylls in the diet to provide cancer protection.

Therapeutic Uses of Chlorophyllin

Internal deodorant

Observations in the 1940s and 1950s that topical SCC had deodorizing effects on foul-smelling wounds led clinicians to administer SCC orally to patients with colostomies and ileostomies in order to control fecal odor (33). While early case reports indicated that SCC doses of 100 to 200 mg/day were effective in reducing fecal odor in ostomy patients (34, 35), a placebo-controlled trial found that 75 mg of oral SCC three times daily was no more effective than placebo in decreasing fecal odor assessed by colostomy patients 36. Several case reports have been published indicating that oral SCC (100-300 mg/day) decreased subjective assessments of urinary and fecal odor in incontinent patients (33, 37).

Trimethylaminuria is a hereditary disorder characterized by the excretion of trimethylamine, a compound with a “fishy” or foul odor. One study in a small number of Japanese patients with trimethylaminuria found that oral SCC (60 mg three times daily) for three weeks significantly decreased urinary trimethylamine concentrations (38).

Wound healing

Research in the 1940s indicated that chlorophyllin slowed the growth of certain anaerobic bacteria in the test tube and accelerated the healing of experimental wounds in animals. These findings led to the use of topical SCC solutions and ointments in the treatment of persistent open wounds in humans (39). During the late 1940s and 1950s, a series of largely uncontrolled studies in patients with slow-healing wounds, such as vascular ulcers and pressure (decubitus) ulcers, reported that the application of topical SCC promoted healing more effectively than other commonly used treatments (40, 41). In the late 1950s, SCC was added to papain and urea-containing ointments used for the chemical debridement of wounds in order to reduce local inflammation, promote healing, and control odor (33). SCC-containing papain/urea ointments are still available in the US by prescription (42). Several studies have reported that such ointments are effective in wound healing (43). A spray formulation of the papain/urea/SCC therapy is also available (44).

Skin conditions

A few small studies have investigated SCC as a topical treatment for various skin conditions. In a pilot study of 10 adults (ages 18-30 years) who had mild-to-moderate acne vulgaris and enlarged facial pores, twice daily application of a 0.1% liposomal SCC gel for three weeks improved a number of clinical parameters of the Global Acne Assessment Scale (i.e., facial oiliness, facial blotchiness, presence and size of facial pores, and number of acne lesions) compared to baseline (45). Additionally, a pilot study in 10 women (ages 40 years or older) with noticeable photodamage and solar lentigines found that twice daily topical application of a gel containing 0.66% SCC complex salts for eight weeks improved various clinical measures, including tactile and visual roughness of facial skin, skin radiance, fine lines, pore size, and overall photodamage (46). A few case reports have also observed some improvement in facial redness and rosacea with application of topical SCC (47).

While the reports from these studies are interesting, placebo-controlled clinical trials are needed to determine whether SCC may have utility in treating various skin conditions.

Sources

Chlorophylls

Chlorophylls are the most abundant pigments in plants, with chlorophyll a being two to four times as prevalent as chlorophyll b (6, 48). Dark-green leafy vegetables like spinach are rich sources of natural chlorophylls. The chlorophyll content of selected vegetables are presented in **Table 1** (49).

Table 1. Chlorophyll Content of Selected Raw Vegetables

Food	Serving	Chlorophyll (mg)
Spinach	1 cup	23.7
Parsley	½ cup	19.0
Cress, garden	1 cup	15.6
Green beans	1 cup	8.3
Arugula	1 cup	8.2
Leeks	1 cup	7.7
Endive	1 cup	5.2
Sugar peas	1 cup	4.8
Chinese cabbage	1 cup	4.1

Food and supplements

Chlorophyll

Green algae like chlorella are often marketed as supplemental sources of chlorophyll. Because natural chlorophyll is not as stable as SCC and is much more expensive, most over-the-counter chlorophyll supplements actually contain sodium copper chlorophyllin.

Sodium copper chlorophyllin

Oral preparations of sodium copper chlorophyllin (also called chlorophyllin copper complex) are available as a dietary supplement and as an over-the-counter drug (Derifil) used to reduce odor from colostomies and ileostomies, or to reduce fecal odor due to incontinence (50). Oral doses of 100 to 300 mg/day in three divided doses have been used to control fecal and urinary odor (see Therapeutic Uses of Chlorophyllin).

In the US, SCC is found in minor quantities in some types of green table olives (51). It is also used as a green color additive in foods like chewing gum (52), as well as in drugs and cosmetics (53).

Zinc chlorophyll derivatives

In US supermarkets, canned green beans thermally processed in a zinc chloride solution to produce zinc chlorophyll derivatives within the green beans themselves are sold under the trademarked name "veri-green" (54). Because zinc chlorophyll derivatives are more robust to heat and acid treatment, they better retain a bright green color as compared to native magnesium-bound chlorophyll (48).

Safety

Natural chlorophylls are not known to be toxic, and no toxic effects have been attributed to chlorophyllin despite more than 50 years of clinical use in humans (11, 33, 39). When taken orally, supplemental chlorophyll or sodium copper chlorophyllin may cause green discoloration of urine or feces, or yellow or black discoloration of the tongue (55). There have also been occasional reports of diarrhea related to oral SCC use. When applied topically to wounds, SCC has been reported to cause mild burning or itching in some cases (56). Oral chlorophyllin may result in false positive results on guaiac card tests for occult blood (57). Since the safety of chlorophyll or chlorophyllin supplements has not been tested in pregnant or lactating women, they should be avoided during pregnancy and lactation.

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Curcumin

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日本語

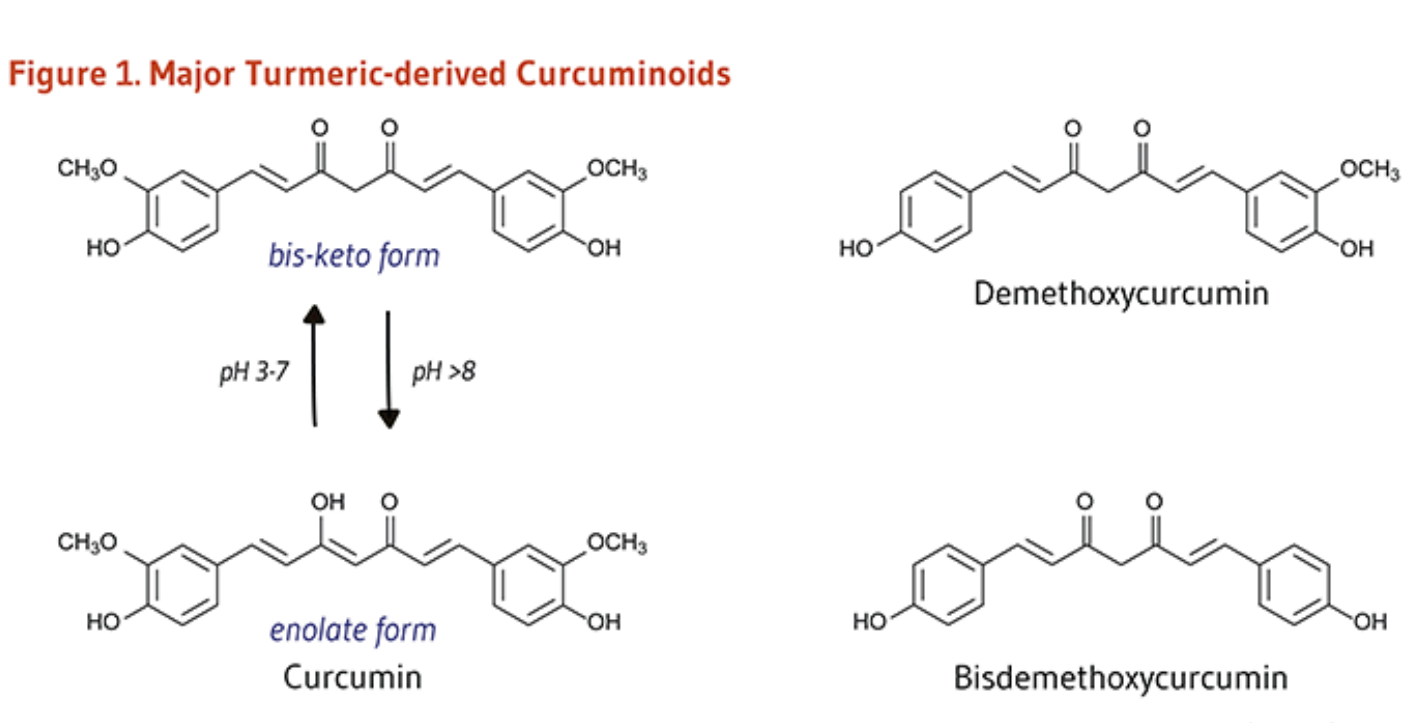
Summary

- Curcumin is a biologically active polyphenolic compound found in turmeric, a spice derived from the rhizomes of the plant *Curcuma longa* Linn. Commonly consumed in Asian countries, turmeric has been used for medicinal purposes for centuries. *(More information)*
- Mounting evidence from preclinical studies shows that curcumin modulates numerous molecular targets and exerts antioxidant, anti-inflammatory, anticancer, and neuroprotective activities. *(More information)*
- In humans, curcumin taken orally is poorly absorbed and rapidly metabolized and eliminated. Therefore, the potential of curcumin as a therapeutic agent is limited by its poor bioavailability. *(More information)*
- Current evidence suggesting that curcumin may help prevent and/or treat colorectal cancer and type 2 diabetes mellitus is very limited. Yet, several clinical trials designed to assess the safety and efficacy of curcumin alone or with first-line treatment in patients with breast, prostate, pancreatic, lung, or colorectal cancer are under way. *(More information)*
- While a few preliminary trials suggested that curcumin may have anti-inflammatory activities in humans, larger randomized controlled trials are still needed to establish the efficacy of curcumin as an anti-inflammatory agent against rheumatoid arthritis, ulcerative colitis, and radiotherapy-induced dermatitis. *(More information)*
- There is currently no substantial evidence showing that curcumin may improve cognitive performance in older adults with or without cognitive impairments. Yet, some preclinical studies have found curcumin prevented or reversed certain pathological features of Alzheimer’s disease (AD). A number of clinical trials designed to assess whether curcumin might help prevent or treat AD are under way. *(More information)*
- Long-term clinical trials are required to confirm whether curcumin could exhibit long-lasting antidepressant effects in patients suffering from major depressive disorder. *(More information)*
- Oral supplementation with curcumin is generally regarded as safe, especially because of its low bioavailability. However, use of curcumin supplements may affect the efficacy or increase the toxicity of a wide range of drugs when taken concurrently. *(More information)*

Introduction

Turmeric is a spice derived from the rhizomes of the tropical plant *Curcuma longa* Linn, which is a member of the ginger family (*Zingiberaceae*). Rhizomes are horizontal underground stems that send out shoots, as well as roots. The bright yellow-orange color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent (1). Other curcuminoids found in turmeric include demethoxycurcumin and bisdemethoxycurcumin (**Figure 1**). In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes for centuries (2). More recently, evidence that curcumin may have anti-inflammatory and anticancer activities has renewed scientific interest in its potential to prevent and treat disease.

Figure 1. Major Turmeric-derived Curcuminoids



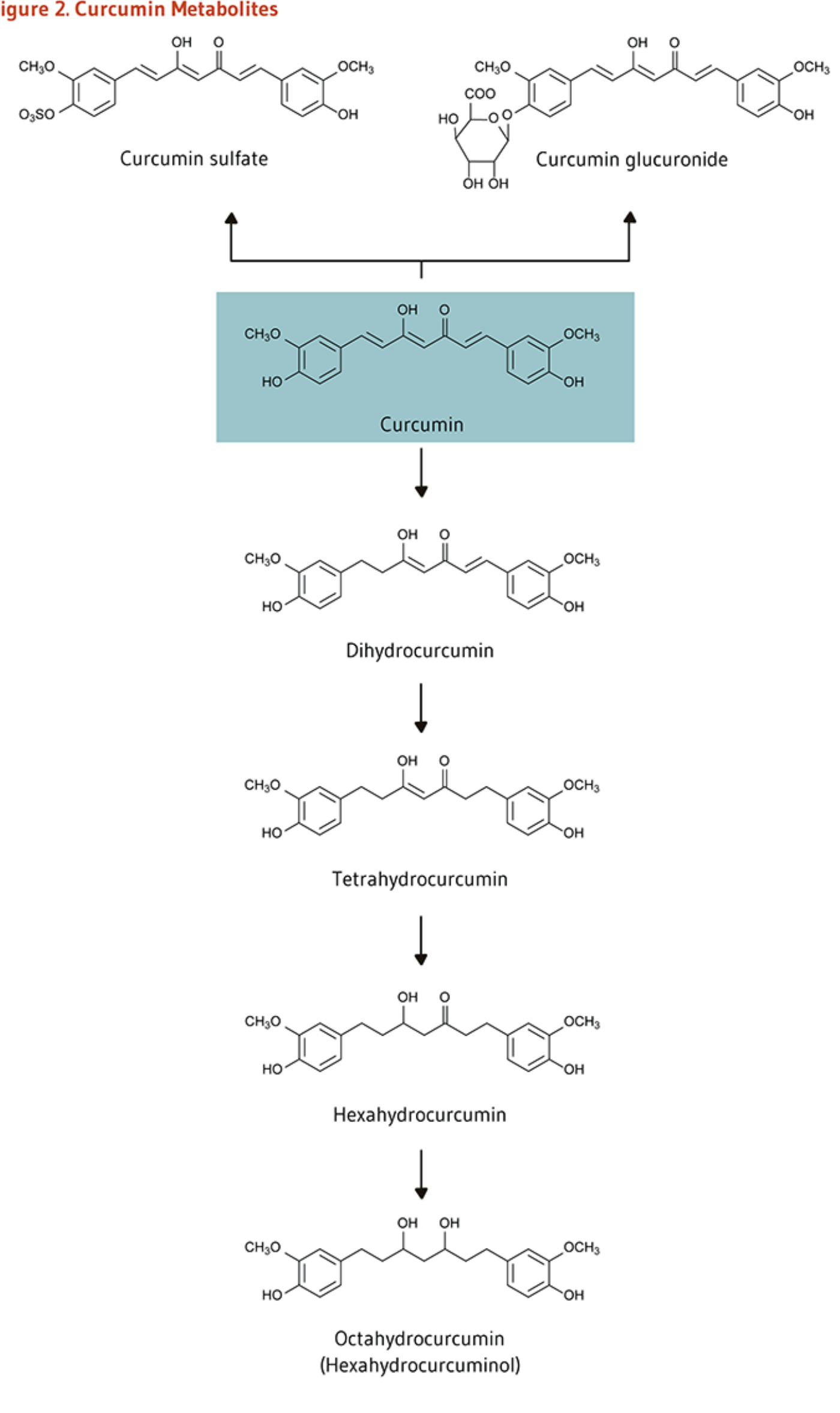
Curcuminoids in turmeric roots are a mixture of three main compounds: curcumin (~77%), demethoxycurcumin (~17%), and bisdemethoxycurcumin (~3%). Curcumin exists in two molecular configurations (known as tautomers): the bis-keto form is predominantly found in neutral and acidic conditions and in a solid phase, while the enolate form is predominately found in alkaline conditions.

Metabolism and Bioavailability

Clinical trials in humans indicate that the systemic bioavailability of orally administered curcumin is relatively low (3-5) and that mostly metabolites of curcumin, instead of curcumin itself, are detected in plasma or serum following oral consumption (6, 7). In the intestine and liver, curcumin is readily conjugated to form curcumin glucuronide and curcumin sulfate or, alternately, reduced to tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin (**Figure 2**) (4). An early clinical trial conducted in Taiwan indicated that serum curcumin concentrations peaked at 0.41 to 1.75 micromoles/liter (μM) one hour after oral doses of 4 to 8 g of curcumin (8). Another clinical trial conducted in the UK found that plasma concentrations of curcumin, curcumin sulfate, and curcumin glucuronide were in the range of 0.01 μM one hour after a 3.6 g oral dose of curcumin (9). Curcumin and its metabolites could not be detected in plasma at doses lower than 3.6 g/day. There is some evidence that orally administered curcumin accumulates in gastrointestinal tissues. For instance, when colorectal cancer patients took 3.6 g/day of curcumin orally for seven days prior to surgery, curcumin was detected in both malignant and normal colorectal tissue (10). In contrast, curcumin was not detected in the liver tissue of patients with liver metastases of colorectal cancer after the same oral dose of curcumin (11), suggesting that oral curcumin administration may not effectively deliver curcumin to tissues outside the gastrointestinal tract.

The safety and efficacy of several curcumin formulations are currently being explored in (pre)clinical settings with the aim of increasing the absorption, bioavailability, and tissue-targeted delivery of curcumin (12-16). Examples of approaches include conjugation to peptide carriers (e.g., to polylactic-co-glycolic acid [PLGA]); complexation with essential oils; coadministration with piperine; and encapsulation into nanoparticles, liposomes, phytosomes, polymeric micelles, and cyclodextrins (reviewed in 17).

Figure 2. Curcumin Metabolites



Biological Activities

Antioxidant activity

Curcumin is an effective scavenger of reactive oxygen species (ROS) and reactive nitrogen species in the test tube (18, 19). However, it is not clear whether curcumin acts as a direct antioxidant *in vivo*. Due to its limited oral bioavailability in humans (see Metabolism and Bioavailability), plasma and tissue curcumin concentrations are likely to be much lower than those of other fat-soluble antioxidants like α-tocopherol (vitamin E). Yet, curcumin taken orally may reach sufficient concentrations in the gastrointestinal tract and protect the intestinal mucosa against oxidative DNA damage (11). In addition to a potentially direct antioxidant activity, curcumin can induce the expression of phase II antioxidant enzymes, including glutamate-cysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis. Glutathione (GSH) is an important intracellular antioxidant that plays a critical role in cellular adaptation to stress (20). Curcumin was found to upregulate the expression of GCL through the activation of different signaling pathways (21). In particular, curcumin increases the expression of GCL and other detoxifying enzymes via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway.

Nrf2-dependent antioxidant pathway

Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol. Keap1 responds to oxidative stress signals by freeing Nrf2. Upon release, Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE) located in the promoter of genes coding for antioxidant/detoxifying enzymes and scavengers. Nrf2/ARE-dependent genes code for numerous mediators of the antioxidant response, including GCL, glutathione S-transferases (GSTs), thioredoxin, NAD(P)H quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) (22). Nrf2-dependent upregulation of HO-1 in curcumin-treated renal tubular epithelial cells challenged with high glucose concentrations was shown to prevent phenotype changes resembling fibrosis and known to occur at an early stage of diabetic renal injury (23). Curcumin also inhibited the progression of fibrosis in liver and lung in animal models of chronic inflammatory diseases (24, 25). Curcumin mitigated the effect of chronic ethanol intake on mouse liver, partly by upregulating Nrf2 target genes coding for NQO-1, HO-1, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) (26). Curcumin treatment also counteracted oxidative damage induced by heavy ion irradiation by upregulating Nrf2 downstream genes for GCL, HO-1, NQO-1, and SOD in the brain of rats (27). Additional studies have demonstrated the ability of curcumin to reduce oxidative stress in different experimental settings via the induction of Nrf2/ARE pathway (reviewed in 22).

Anti-inflammatory activity

Curcumin has been shown to inhibit mediators of the inflammatory response, including cytokines, chemokines, adhesion molecules, growth factors, and enzymes like cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). Nuclear factor-kappa B (NF-κB) is a transcription factor that binds DNA and induces the transcription of the COX-2 gene, other pro-inflammatory genes, and genes involved in cell proliferation, adhesion, survival, and differentiation. The anti-inflammatory effects of curcumin result from its ability to inhibit the NF-κB pathway, as well as other pro-inflammatory pathways like the mitogen-activated protein kinase (MAPK)- and the Janus kinase (JAK)/Signal transducer and activator of transcription (STAT)-dependent signaling pathways (28). Inhibition of dextran sulfate sodium (DSS)-induced colitis by curcumin in mice has been associated with a downregulation of the expression of p38-MAPK and pro-inflammatory cytokine TNF-α and a reduction of myeloperoxidase (MPO) activity, a marker of neutrophil infiltration in intestinal mucosa (29). Curcumin has also been shown to improve colitis by preventing STAT3 activation and STAT3-dependent induction of cell proliferation in mouse colon (30). Moreover, curcumin was shown to attenuate the immune response triggered by collagen injections in a mouse model of rheumatoid arthritis, partly by blocking the proliferation of T lymphocytes in mouse splenocytes (31). In addition, curcumin has been found to reduce the secretion of TNF-α and IL-1β and the production of COX-2-induced prostaglandin G2. In one study, curcumin inhibited the secretion of matrix metalloproteins (MMPs) — responsible for the degradation of the synovial joints — in human fibroblast-like synoviocytes (31) and in human articular chondrocytes (32). Curcumin has also been found to alleviate neuro-inflammation in a mouse model of traumatic brain injury, reducing macrophage and microglial activation and increasing neuronal survival (33).

Anticancer activity

Effects on biotransformation enzymes

Some compounds are not carcinogenic until they are metabolized in the body by phase I biotransformation enzymes, such as enzymes of the cytochrome P450 (CYP) family (34). Primarily based on evidence from rodent studies, it is thought that curcumin may inhibit procarcinogen bioactivation and help prevent cancer by inhibiting the activity of multiple CYP enzymes in humans (35-37). Curcumin may also increase the activity of phase II detoxification enzymes, such as GSTs and quinone reductase (QR) (see also Nrf2-dependent antioxidant pathway) (35, 38, 39). However, it is important to note that the effect of curcumin on biotransformation enzymes may vary depending on the route of administration, the dose, and the animal model. In addition, curcumin intakes ranging from 0.45 to 3.6 g/day for up to four months did not increase leukocyte GST activity in humans (9).

Inhibition of proliferation and induction of apoptosis

Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or for activation of pathways leading to programmed cell death (apoptosis) if the damage is irreparable (40). Defective cell-cycle regulation may result in the propagation of mutations that contribute to the development of cancer. Unlike normal cells, cancer cells proliferate rapidly and are unable to respond to cell death signals that initiate apoptosis. Curcumin has been found to induce cell-cycle arrest and apoptosis by regulating a variety of cell-signaling pathways (3, 41-45). For example, the inhibition of cell proliferation by curcumin has been associated with the Nrf2-dependent downregulation of DNA repair-specific flap endonuclease 1 (Fen1) in breast cancer cells in culture (46). Curcumin has been shown to induce p53-dependent or -independent apoptosis depending on the cancer cell type (47). In a panel of cancer cell lines, p53-independent apoptosis induced by curcumin was mediated by the rapid increase of ROS and the activation of MAPK and c-jun kinase (JNK) signaling cascades (48). Inhibition of NF-κB signaling by curcumin also suppresses proliferation and induces apoptosis in cancer cells (47).

Inhibition of tumor invasion and angiogenesis

Malignant and aggressive forms of cancer can invade surrounding tissues and spread to distant tissues once cancer cells have acquired the ability to leave the primary site (reduced cell-to-cell adhesion and loss of polarity), migrate, and disseminate. Epithelial-mesenchymal transition (EMT) is the process by which epithelial cells acquire the ability to migrate and invade through downregulating proteins like E-cadherin and γ-catenin and expressing mesenchymal markers like MMPs, N-cadherin, and vimentin. In breast cancer cells, curcumin prevented EMT-associated morphological changes induced by lipopolysaccharide (LPS) while upregulating E-cadherin and downregulating vimentin. It was further shown that curcumin inhibited NF-κB/Snail signaling involved in LPS-induced EMT (49). In another study, curcumin increased the expression of the small non-coding RNA miR181b, which then downregulated proinflammatory cytokines, CXCL1 and CXCL2, as well as MMPs, thereby reducing the metastatic potential of breast cancer cells. Curcumin inhibited IL-6-induced proliferation, migration, and invasiveness of human small cell lung cancer (SCLC) cells by reducing JAK/STAT3 phosphorylation (i.e., activation) and downstream genes coding for cyclin B1, survivin, Bcl-X$_L$, MMPs, intercellular adhesion molecule 1 (ICAM-1), and vascular endothelial growth factor (VEGF) (30).

Curcumin was found to exert its anticancer activities in many different types of cancer cells by regulating a variety of signaling pathways (reviewed in 2, 47).

Neuroprotective activity

In Alzheimer’s disease (AD), a peptide called β-amyloid (Aβ peptide) aggregates into oligomers and fibrils and forms deposits known as amyloid (or senile) plaques outside neurons in the hippocampus and cerebral cortex of patients. Another feature of AD is the accumulation of intracellular neurofibrillary tangles formed by phosphorylated Tau protein (50). Abnormal microglial activation, oxidative stress, and neuronal death are also associated with the progression of the disease. Curcumin has been found to inhibit Aβ fibril formation and extension and to destabilize preformed fibrils *in vitro* (51-53). Metal chelation by curcumin might interfere with metal ion (Cu^{2+}/Zn^{2+})-induced Aβ aggregation. Curcumin might also affect the trafficking of Aβ peptide precursor (APP) and the generation of Aβ peptides from APP (54, 55). Abnormally activated microglia and hypertrophic astrocytes around amyloid plaques in AD brains release cytotoxic molecules, such as proinflammatory cytokines and ROS, which enhance Aβ formation and deposition and further damage neurons. Curcumin was found to reduce the inflammatory response triggered by Aβ peptide-induced microglial activation and increase neuronal cell survival (56). When injected into the carotid artery of a transgenic mouse model of AD, curcumin was found to cross the blood-brain barrier, bind to amyloid plaques, and block the formation of Aβ oligomers and fibrils (53). In other animal models of AD, dietary curcumin decreased biomarkers of inflammation and oxidative damage, increased Aβ peptide clearance by macrophages, dismantled amyloid plaques in the brain, stimulated neuronal cell growth in the hippocampus, and improved Aβ-induced memory deficits (reviewed in 57).

Note: It is important to keep in mind that some of the biological activities discussed above were observed in cultured cells and animal models exposed to curcumin at concentrations unlikely to be achieved in cells of humans consuming curcumin orally (see Metabolism and Bioavailability).

Disease Prevention

Cancer

Oral curcumin administration has been found to inhibit the development of chemically-induced cancer in animal models of oral (58, 59), stomach (60, 61), liver (62), and colon (63-65) cancer. Apc$^{Min/+}$ mice have a mutation in the Apc (adenomatous polyposis coli) gene similar to that in humans with familial adenomatous polyposis, a genetic condition characterized by the development of numerous colorectal adenomas (polyps) and a high risk for colorectal cancer. Oral curcumin administration has been found to inhibit the development of intestinal adenomas in Apc$^{Min/+}$ mice (66, 67). Despite promising results in animal studies, there is presently little evidence that high intakes of curcumin or turmeric are associated with decreased cancer risk in humans. A 30-day phase II clinical trial in 40 smokers with at least eight rectal aberrant crypt foci (ACF; precancerous lesions) found that the number of ACF was significantly lower with a daily supplementation with 4 g/day of curcumin compared to 2 g/day (68). Several controlled clinical trials in humans designed to evaluate the effect of oral curcumin supplementation on precancerous colorectal lesions, such as adenomas, are under way (69).

Type 2 diabetes mellitus

Oxidative stress and inflammation have been implicated in the pathogenesis of type 2 diabetes mellitus and related vascular complications. A large body of preclinical evidence suggests that the antioxidant, anti-inflammatory, and glucose-lowering activities of curcumin and its analogs may be useful in the prevention and/or treatment of type 2 diabetes (70). In a nine-month, randomized, double-blind, placebo-controlled study in 237 subjects with impaired glucose tolerance (pre-diabetes), no progression to overt diabetes was reported with a daily ingestion of a mixture of curcuminoids (0.5 g), while 16.4% of placebo-treated participants developed diabetes (71). In addition, curcumin supplementation was shown to reduce insulin resistance and improve measures of pancreatic β-cell function and glucose tolerance. In an eight-week, randomized, placebo-controlled study in 67 individuals with type 2 diabetes, oral curcumin (a mixture of all three major curcuminoids; 0.6 g/day) failed to significantly lower the level of glycated hemoglobin A1c (HbA1c; a measure of glycemic control), plasma fasting glucose, total serum cholesterol, LDL-cholesterol, and serum triglycerides (72). Yet, supplemental curcumin was found to be as effective as lipid-lowering drug atorvastatin (10 mg/day) in reducing circulating markers of oxidative stress (malondialdehyde) and inflammation (endothelin-1, TNFα, IL-6) and in improving endothelial function. Another randomized controlled trial also reported that oral curcumin supplementation (1.5 g/day) for six months improved endothelial function, insulin sensitivity, and metabolic markers associated with atherogenesis (plasma triglycerides, visceral fat, total body fat) in participants with type 2 diabetes (73). Finally, in a two-month randomized, double-blind, placebo-controlled study in 40 individuals with type 2 diabetic nephropathy (kidney disease), daily curcumin ingestion (66.3 mg) significantly reduced urinary concentrations of proteins and inflammation markers (TGF-β, IL-8), suggesting that curcumin might be helpful with slowing the progression of kidney damage and preventing kidney failure (74). Larger trials are needed to assess whether curcumin could be useful in the prevention or management of type 2 diabetes and vascular complications.

Disease Treatment

Cancer

The ability of curcumin to regulate a variety of signaling pathways involved in cell growth, apoptosis, invasion, metastasis, and angiogenesis in preclinical studies elicited scientific interest in its potential as an anticancer agent in tumor therapy (75). To date, most of the controlled clinical trials of curcumin supplementation in cancer patients have been phase I trials, which are aimed at determining feasibility, tolerability, safety, and providing early evidence of efficacy (76). A phase I clinical trial in patients with advanced colorectal cancer found that doses up to 3.6 g/day for four months were well tolerated, although the systemic bioavailability of oral curcumin was low (77). When colorectal cancer patients with liver metastases took 3.6 g/day of curcumin orally for seven days, trace levels of curcumin metabolites were measured in liver tissue, but curcumin itself was not detected (11). In contrast, curcumin was measurable in normal and malignant colorectal tissue after patients with advanced colorectal cancer took 3.6 g/day of curcumin orally for seven days (10). In a pilot trial in patients awaiting gastrointestinal endoscopy or colorectal cancer resection, the administration of a mixture of three major curcuminoids (2.35 g/day for 14 days) resulted in detectable amounts of curcumin in colonic mucosa (mean concentration, 48.4 μg/g of tissue), demethoxycurcumin (7.1 μg/g), and bisdemethoxycurcumin (0.7 μg/g) (78).

While these findings suggested that oral curcumin may likely be more effective as a therapeutic agent in cancers of the gastrointestinal tract than of other tissues, some phase I/II trials have also examined whether supplemental curcumin may confer additional benefits to conventional drugs against different types of cancer. Combining curcumin with anticancer drugs like gemcitabine in pancreatic cancer (79, 80), docetaxel in breast cancer (81), and imatinib in chronic myeloid leukemia (82) may be safe and well tolerated. A recent single-arm, phase II trial combining three cycles of docetaxel/prednisone and curcumin (6 g/day) was carried out in 26 patients with castration-resistant prostate cancer (83). The level of prostate-specific antigen (PSA) was decreased in most patients and was normalized in 36% of them, and the co-administration of curcumin with drugs showed no toxicity beyond adverse effects already related to docetaxel monotherapy. Many registered phase I/II clinical trials designed to investigate the effectiveness of curcumin alone or with first-line treatment in patients with breast, prostate, pancreatic, lung, or colorectal cancer are under way (69).

Inflammatory diseases

Although curcumin has been demonstrated to have anti-inflammatory and antioxidant activities in cell culture and animal studies, few randomized controlled trials have examined the efficacy of curcumin in the treatment of inflammatory conditions. A placebo-controlled trial in 40 men who had surgery to repair an inguinal hernia or hydrocele found that oral curcumin supplementation (1.2 g/day) for five days was more effective than placebo in reducing post-surgical edema, tenderness and pain, and was comparable to phenylbutazone therapy (300 mg/day) (84).

Rheumatoid arthritis

A preliminary intervention trial that compared curcumin with a nonsteroidal anti-inflammatory drug (NSAID) in 18 patients with rheumatoid arthritis (RA) found that improvements in morning stiffness, walking time, and joint swelling after two weeks of curcumin supplementation (1.2 g/day) were comparable to those experienced after two weeks of phenylbutazone (NSAID) therapy (300 mg/day) (85). In a more recent randomized, open-label study in 45 RA patients, supplementation with a mixture of all three major curcuminoids (0.5 g/day for eight weeks) was found to be as effective as diclofenac (NSAID; 50 mg/day) in reducing measures of disease activity, tenderness, and swelling joints (86). Larger randomized controlled trials are needed to determine whether oral curcumin supplementation is effective in the treatment of RA.

Radiation dermatitis

Radiation-induced skin inflammation occurs in most patients receiving radiation therapy for sarcoma, lung, breast, or head and neck cancer. One randomized, double-blind, placebo-controlled trial in 30 women prescribed radiation therapy for breast carcinoma *in situ* reported a reduction of radiation-induced dermatitis severity and moist desquamation with a supplemental curcuminoid mixture (6 g/day for four to seven weeks). Curcumin failed to reduce skin redness and radiation-induced pain at the site of treatment (87).

Ulcerative colitis

Ulcerative colitis (UC) is a long-term condition characterized by diffuse and superficial inflammation of the colonic mucosa. Disease activity may fluctuate between periods of remission and periods of relapse. Preliminary evidence suggests that curcumin might be useful as an add-on therapy to control disease activity. One multicenter, randomized, double-blind, placebo-controlled study has examined the efficacy of curcumin enema (2 g/day) in the prevention of relapse in 82 patients with quiescent UC (88). Six-month treatment with curcumin significantly reduced measures of disease activity and severity and resulted in a lower relapse rate than with placebo in subjects on standard-of-care medication (sulfasalazine or mesalamine); yet, there was no difference in the proportion of patients who experienced relapse six months after curcumin was discontinued (88). In another randomized controlled trial in active UC patients treated with mesalamine, the percentage of patients in clinical remission was significantly higher after a one-month treatment with oral curcumin (3 g/day) than with placebo (89). Larger trials are needed to ensure that curcumin can be safely used with conventional UC treatments and to further support its potential therapeutic benefits for relapsing-remitting UC.

Oral health

Emerging evidence suggests that curcumin has anti-inflammatory and antimicrobial properties that could be beneficial in the treatment of certain diseases of the oral cavity. For example, the topical application of a curcumin gel was found to reduce gingival bleeding and periodontal bacteria after conventional periodontal therapy (scaling and root planing) (90-92). A mouthwash containing curcumin was also found to be as effective as chlorhexidine in reducing inflammation in individuals who underwent periodontal therapy for gingivitis (93).

Oral submucous fibrosis

Any part of the oral cavity may be affected by oral submucous fibrosis (OSMF), a currently incurable condition especially prevalent in Southeast Asia and India. OSMF is characterized by the formation of excess fibrous tissue (fibrosis) that leads to stiffness of the mucosa and restricted mouth opening. A few recent intervention studies showed that curcumin could improve some symptoms, such as burning sensations and reduced mouth opening (reviewed in 94). In an open-label intervention study in 40 OSMF patients randomized to receive either the conventional treatment (weekly intra-lesional injections of steroids) or daily oral administration of a *Curcuma longa* Linn extract (600 mg/day) for three months, the burning sensation significantly improved in the curcumin-treated group, while tongue protrusion was reduced with conventional therapy. No differences between the two treatment groups were seen with respect to mouth opening (95). A six-month follow-up of the effect of oral curcumin (2 g/day) in OSMF patients treated for three months found that curcumin outperformed steroid ointment in its ability to increase maximum mouth opening and to reduce self-reported burning sensation (96). Further studies should assess the appropriate dose of curcumin to achieve the greatest benefits and determine whether curcumin can enhance the effect of standard-of-care treatment in limiting OSMF disease progression.

Cognitive decline and Alzheimer’s disease

Alzheimer’s disease (AD) is a form of dementia characterized by extracellular deposition of β-amyloid plaques, intracellular formation of neurofibrillary tangles, and neuronal loss, eventually leading to brain atrophy and cognitive impairment in affected individuals (57). When injected into the carotid artery, curcumin was found to cross the blood-brain barrier in an animal model of AD (53), though it is not known whether curcumin taken orally can reach the blood-brain barrier at sufficient concentrations and impede cognitive decline in humans. As a result of promising findings in animal models (see Neuroprotective activity), a few recent clinical trials have examined the effect of oral curcumin supplementation on cognition in healthy older adults and AD patients (57). A randomized, double-blind, placebo-controlled trial in 60 healthy older adults (mean age, 68.5 years) investigated whether acute (80 mg) or chronic (80 mg/day for 4 weeks) oral intake of curcumin could improve their ability to cope with the mental stress and change in mood usually associated with undergoing a battery of cognitive tests (97). A significant reduction in mental fatigue and higher levels of calmness and contentedness following cognitive test sessions were observed in individuals who consumed curcumin (either acutely or chronically) compared to the placebo group. Additionally, the results of cognitive ability tests suggested that curcumin treatment had limited benefits on cognitive function, as shown by better scores in measures of sustained attention and working memory compared to placebo (97).

The results of a six-month trial in 27 patients with AD found that oral supplementation with up to 4 g/day of curcumin — containing all three major curcuminoids — was safe (6). Yet, measures of cognitive performance (using the Mini Mental State Examination [MMSE] scoring scale) and levels of F$_2$-isoprostanes (oxidative stress markers) and antioxidants in blood were not found to be significantly different between curcumin- and placebo-treated subjects at the end of the intervention period. In another six-month, randomized, double-blind, placebo-controlled study of subjects with mild-to-moderate AD, curcumin failed to improve cognitive test scores and to reduce blood and cerebrospinal fluid (CSF) concentrations of β-amyloid peptide, CSF concentrations of total and phosphorylated Tau protein, and CSF concentrations of F$_2$-isoprostanes (98).

Despite the lack of encouraging results from completed trials, several randomized controlled studies are under way to determine whether supplemental curcumin has the ability to reverse or prevent cognitive deficits in both healthy and cognitively impaired individuals (57).

Major depressive disorder

Major depressive disorder (MDD) is a neuropsychiatric disorder associated with abnormal neurotransmission; it is primarily treated with drugs that improve the bioavailability of neurotransmitters like serotonin, noradrenaline, and dopamine in the brain (99). Characteristics of MDD also include alterations in the hypothalamus-pituitary-adrenal axis, increased neuroinflammation, defective neurogenesis, and neuronal death.

A few clinical studies have examined the effect of curcumin alone or with conventional antidepressant drugs in MDD patients. A recent meta-analysis of six randomized controlled trials found that supplementation with curcumin significantly reduced depression symptoms (100). However, in one of the studies included in this meta-analysis — a double-blind, controlled study in 56 adults diagnosed with MDD — curcumin treatment (~880 mg/day of curcuminoids) for eight weeks was no more effective than placebo in reducing self-reported depression- and anxiety-related symptoms (101). Significant improvements in the severity and frequency of specific depression-related symptoms only occurred after four weeks of treatment, suggesting that a longer treatment period might be needed to uncover the antidepressant effects of curcumin (100, 101). In another randomized, placebo-controlled trial, supplemental curcumin (330 mg/day) for five weeks failed to relieve depressive symptoms in patients treated with conventional antidepressants (102). In contrast, in a six-week, randomized, single-blinded, placebo-controlled study in 60 MDD patients, supplemental curcumin (~880 mg/day of curcuminoids) alone yielded a similar response rate to the antidepressant, fluoxetine (a serotonin reuptake inhibitor [Prozac]; 20 mg/day) in terms of depressive symptoms; no additional effect was observed when both curcumin and fluoxetine treatments were combined (103). Moreover, in a randomized controlled study in 100 participants taking escitalopram (a serotonin reuptake inhibitor [Lexapro]; 5 to 15 mg/week), supplemental curcumin (1,000 mg/day) for six weeks increased the antidepressant effect of the medication (104). Curcumin also induced a reduction in plasma concentrations of inflammatory markers and an increase in plasma concentrations of brain-derived neurotrophic factor compared to placebo (antidepressant drug alone) (104).

Larger clinical trials are needed to address the long-term effect of curcumin in subjects with major depression.

Premenstrual syndrome

Premenstrual syndrome (PMS) refers to a range of emotional (e.g., irritability, anxiety), behavioral (e.g., fatigue, insomnia), and physical symptoms (e.g., breast tenderness, headache) occurring prior to the monthly menstrual period in up to 90% of premenopausal women. In a recent randomized, double-blind, placebo-controlled trial in 70 women with PMS, the daily supplementation with 0.2 g of curcumin for 10 days during three consecutive menstrual cycles significantly reduced overall PMS severity, as assessed by a composite measure of all emotional, behavioral, and physical symptoms (105). Additional trials are necessary to evaluate the efficacy of curcumin in the management of PMS.

Sources

Food sources

Turmeric is the dried ground rhizome of *Curcuma longa* Linn (106). It is used as a spice in Indian, Southeast Asian, and Middle Eastern cuisines. Curcuminoids comprise about 2%-9% of turmeric (107). Curcumin is the most abundant curcuminoid in turmeric, providing about 75% of the total curcuminoids, while demethoxycurcumin and bisdemethoxycurcumin generally represent 10%-20% and less than 5% of the total curcuminoids, respectively (108). Curry powder contains turmeric along with other spices, but the amount of curcumin in curry powders is variable and often relatively low (109). Curcumin extracts are also used as food-coloring agents (110).

Supplements

Commercial curcumin is usually a mixture of curcumin, demethoxycurcumin, and bisdemethoxycurcumin (see **Figure 1** above). Curcuminoid extracts are available as dietary supplements without a prescription in the US. The labels of a number of these extracts state that they are standardized to contain 95% curcuminoids, although such claims are not strictly regulated by the US Food and Drug Administration (FDA). Some curcumin preparations also contain piperine, which may increase the bioavailability of curcumin by inhibiting its metabolism (108). However, piperine may also affect the metabolism of drugs (see Drug interactions). Optimal doses of curcumin for cancer chemoprevention or therapeutic uses have not been established. It is unclear whether doses less than 3.6 g/day are biologically active in humans (see Metabolism and Bioavailability). Curcuminoid-containing supplements taken on an empty stomach may cause gastritis and peptic ulcer disease (108).

Safety

Adverse effects

In the United States, turmeric is generally recognized as safe (GRAS) by the FDA as a food additive (110). An increase in gallbladder contractions was observed in 12 healthy people supplemented with single doses of 20 to 40 mg of curcumin (111, 112). Yet, serious adverse effects have not been reported in humans taking high doses of curcumin. A dose escalation trial in 24 adults found that single oral dosages up to 12 g were safe, and adverse effects, including diarrhea, headache, rash, yellow stool, were not related to dose (7). In a phase I trial in Taiwan, curcumin supplementation up to 8 g/day for three months was reported to be well tolerated in patients with precancerous conditions or noninvasive cancer (8). Another clinical trial in the UK found that curcumin supplementation ranging from 0.45 to 3.6 g/day for four months was generally well tolerated by people with advanced colorectal cancer, although two participants experienced diarrhea and another reported nausea (9). Increases in serum alkaline phosphatase and lactate dehydrogenase were also observed in several participants, but it was not clear whether these increases were related to curcumin supplementation or cancer progression (3). In an open-label phase II trial, curcumin treatment (8 g/day) in combination with the anticancer drug gemcitabine was associated with severe abdominal pain in 7 out of 17 patients with advanced pancreatic cancer, leading to the treatment being discontinued in five patients while curcumin dosage was reduced to 4 g/day in two patients (79).

Pregnancy and lactation

Although there is no evidence that dietary consumption of turmeric as a spice adversely affects pregnancy or lactation, the safety of curcumin supplements in pregnancy and lactation has not been established.

Drug interactions

Curcumin has been found to inhibit platelet aggregation *in vitro* (113, 114), suggesting a potential for curcumin supplementation to increase the risk of bleeding in people taking anticoagulant or antiplatelet medications, such as aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), and warfarin (Coumadin). In cultured breast cancer cells, curcumin inhibited apoptosis induced by the chemotherapeutic agents, camptothecin, mechlorethamine, and doxorubicin at concentrations of 1 to 10 μM (115). In an animal model of breast cancer, dietary curcumin inhibited cyclophosphamide-induced tumor regression. Yet, it is not known whether oral curcumin administration will result in breast tissue concentrations that are high enough to inhibit cancer chemotherapeutic agents in humans (11). Curcuminoids may interfere with the activity of efflux drug transporters of the ATP-binding cassette (ABC) family, including P-glycoprotein, multidrug resistance protein (MRP), and breast cancer-resistant protein (BCRP), which function as ATP-dependent efflux pumps that actively regulate the excretion of a number of drugs limiting their systemic bioavailability (116, 117). Curcumin was also found to affect the activity of phase I biotransformation enzymes like cytochrome P450 (CYP) 3A4 (CYP3A4) (118), which catalyzes the metabolism of about one-half of all marketed drugs in the US (119). In healthy Japanese volunteers, curcumin (2 g) was found to increase plasma sulfasalazine concentration following the administration of a therapeutic dose (2 g) of the anti-rheumatic drug sulfasalazine (Salazopyrin, Azulfidine) (120).

Some curcumin supplements also contain piperine to increase the bioavailability of curcumin. Piperine may also interfere with efflux drug transporters and phase I cytochrome P450 enzymes and increase the bioavailability and slow the elimination of a number of drugs, including phenytoin (Dilantin), propranolol (Inderal), theophylline, and carbamazepine (Tegretol) (121-123).

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Flavonoids

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日本語

Summary

- Flavonoids are a large family of polyphenolic plant compounds. Six major subclasses of flavonoids, namely anthocyanidins, flavan-3-ols, flavonols, flavanones, flavones, and isoflavones, flavonols are the most widespread in the human diet. *(More information)*
- Dietary flavonoids are naturally occurring in fruit, vegetables, chocolate, and beverages like wine and tea. There has been much interest in the potential health benefits of flavonoids associated with fruit- and vegetable-rich diets. *(More information)*
- The physicochemical properties of flavonoids influence their metabolic fate, i.e., their digestion, absorption, and biotransformation. The bioavailability of these polyphenols *in vivo* is a major determinant in their ability to exert biological activities relevant to human health. *(More information)*
- Many of the biological effects of flavonoids appear to be related to their ability to modulate a number of cell-signaling cascades. Flavonoids have been shown to exhibit antiinflammatory, antithrombogenic, antidiabetic, anticancer, and neuroprotective activities through different mechanisms of action *in vitro* and in animal models. *(More information)*
- Accumulating evidence from randomized controlled trials suggests that consumption of flavan-3-ols and anthocyanidins can be beneficial for metabolic and cardiovascular health. *(More information)*
- The results of small-scale randomized controlled trials suggest that consumption of flavonoid-rich food and beverages containing anthocyanins or flavan-3-ols may improve vascular endothelial function. As yet, it is not known whether these acute improvements result in long-term reductions in risk of cardiovascular disease. *(More information)*
- Promising findings in randomized controlled studies indicate that supplementation with flavan-3-ols or anthocyanidins may improve glycemic control in subjects at-risk or diagnosed with type 2 diabetes mellitus. *(More information)*
- Despite promising results in animal studies, only a limited number of observational studies have reported potential cancer preventive effects of flavonoids in humans. Higher intakes of soy isoflavones may be associated with reduced risks of breast cancer in postmenopausal women and prostate cancer in men. *(More information)*
- Evidence suggesting that some flavonoids or flavonoid-rich foods may enhance cognitive function is currently limited, and it is not yet known whether their consumption could lower the risk of cognitive impairments and dementia in humans. *(More information)*
- High intakes of dietary flavonoids are generally regarded as safe, especially because of their low bioavailability. However, flavonoid supplements may affect the action of anticoagulants and increase the toxicity of a wide range of drugs when taken concurrently. *(More information)*

Introduction

Flavonoids are a large family of over 5,000 hydroxylated polyphenolic compounds that carry out important functions in plants, including attracting pollinating insects; combating environmental stresses, such as microbial infection; and regulating cell growth (1). Their bioavailability and biological activities in humans appear to be strongly influenced by their chemical nature. Since the 1990s, there has been a growing interest in dietary flavonoids due to their likely contribution to the health benefits of fruit- and vegetable-rich diets. This article reviews some of the scientific evidence regarding the role of dietary flavonoids in health promotion and disease prevention in humans; it is not meant to be a comprehensive review on every health topic studied.

Flavonoid Subclasses

Flavonoids are classified into 12 major subclasses based on chemical structures, six of which, namely anthocyanidins, flavan-3-ols, flavonols, flavones, flavanones, and isoflavones (**Table 1** and **Figures 1-9**) are of dietary significance. Glycosylated flavonols (bound to at least one sugar molecule) are the most widely distributed flavonoids in the diet (2, 3).

Table 1. Common Dietary Flavonoids
(Select the highlighted text to see chemical structures.)

Flavonoid Subclass	Dietary Flavonoids (aglycones)	Some Common Food Sources (see also Sources)
Anthocyanidins*	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Red, blue, and purple berries; red and purple grapes; red wine
Flavan-3-ols	*Monomers (Catechins)*: (+)-Catechin, (-)-Epicatechin, (-)-Epigallocatechin, (+)-Gallocatechin; and their gallate derivatives	Teas (particularly white, green, and oolong), cocoa-based products, grapes, berries, apples
	Dimers and Polymers: Proanthocyanidins#	Apples, berries, cocoa-based products, red grapes, red wine
	Theaflavins, Thearubigins	Black tea
Flavonols	Isorhamnetin, Kaempferol, Myricetin, Quercetin	Onions, scallions, kale, broccoli, apples, berries, teas
Flavones	Apigenin, Luteolin, Baicalein, Chrysin	Parsley, thyme, celery, hot peppers
Flavanones	Eriodictyol, Hesperetin, Naringenin	Citrus fruit and juices, e.g., oranges, grapefruits, lemons
Isoflavones	Daidzein, Genistein, Glycitein, Biochanin A, Formononetin	Soybeans, soy foods, legumes
*Anthocyanidins with one or more sugar moieties (anthocyanidin glycosides) are called anthocyanins. #Proanthocyanidin oligomers formed from (+)-catechin and (-)-epicatechin subunits are called procyanidins.		

For more detailed information on the health effects of isoflavones, a subclass of flavonoids with estrogenic activity, see the article on Soy Isoflavones.

For more information on the health benefits of foods that are rich in flavonoids, see the articles on Fruit and Vegetables, Legumes, and Tea.

Figure 1. Basic Structures of Flavonoid Subclasses

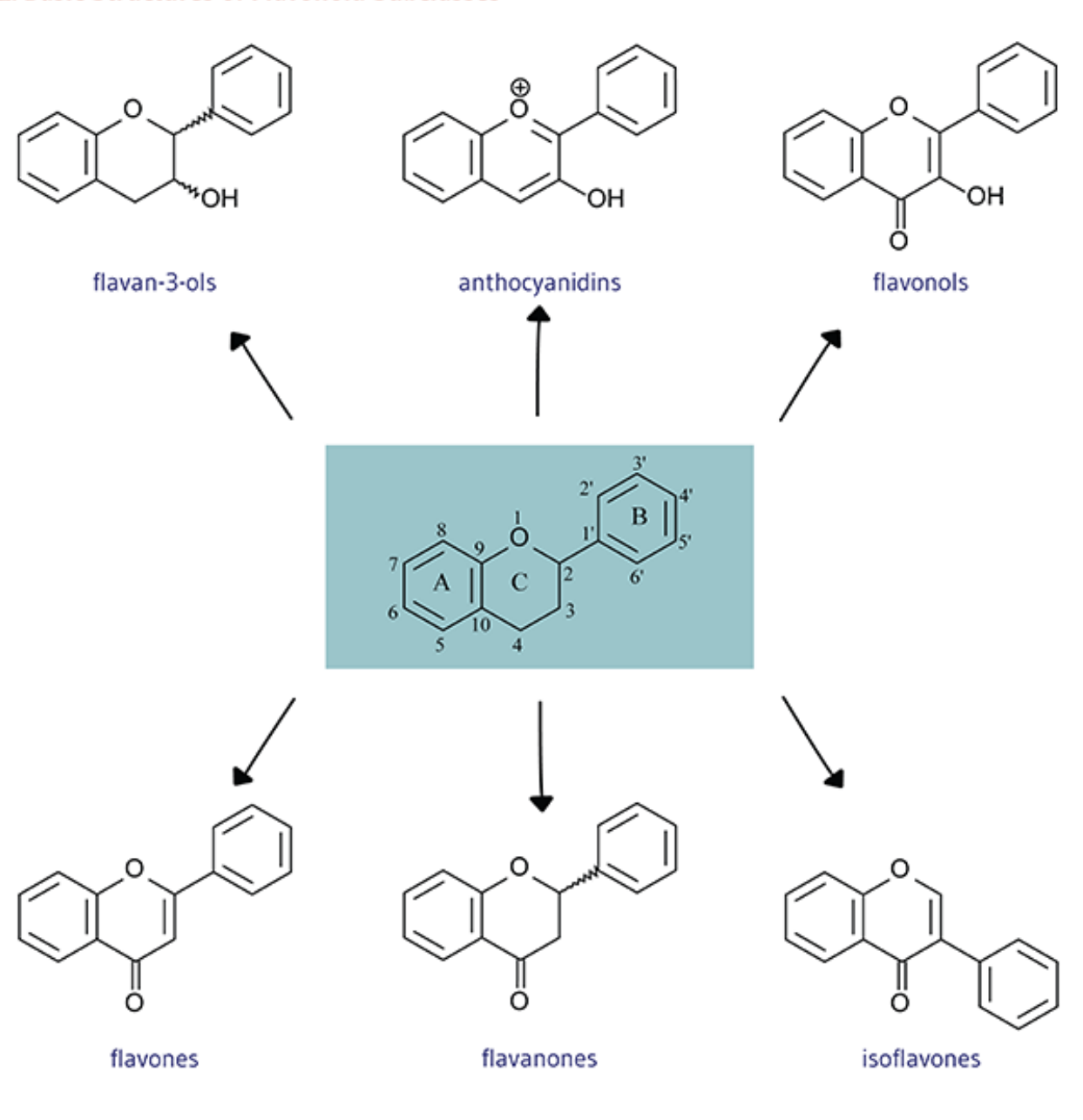


Figure 2. Chemical Structures of Some Flavan-3-ol Monomers (Catechins)

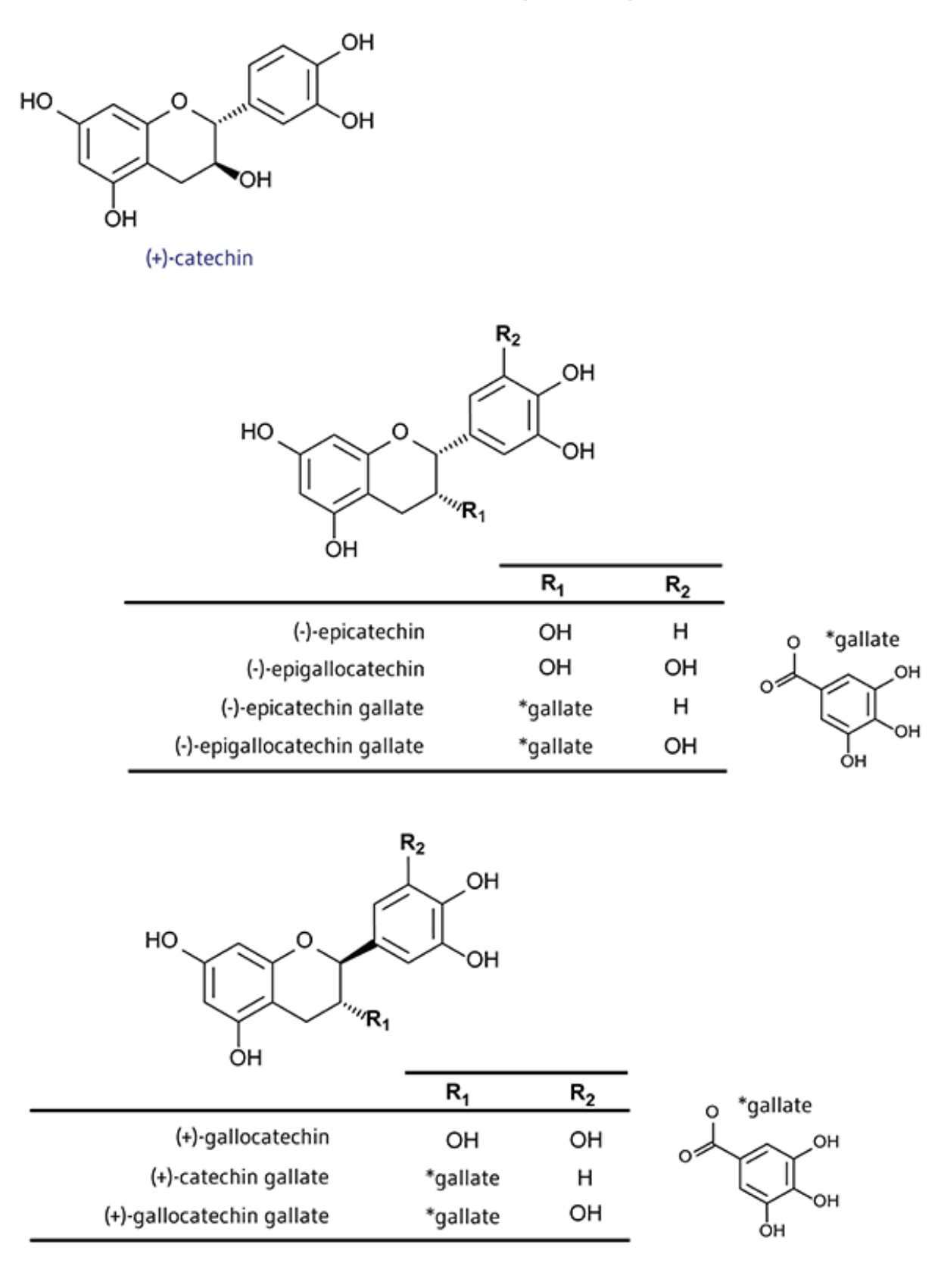

(+)-catechin
R1
R2
(-)-epicatechin OH H
(-)-epigallocatechin OH OH
(-)-epicatechin gallate *gallate H
(-)-epigallocatechin gallate *gallate OH
*gallate
(+)-gallocatechin OH OH
(+)-catechin gallate *gallate H
(+)-gallocatechin gallate *gallate OH

Figure 3. Chemical Structures of Theaflavins

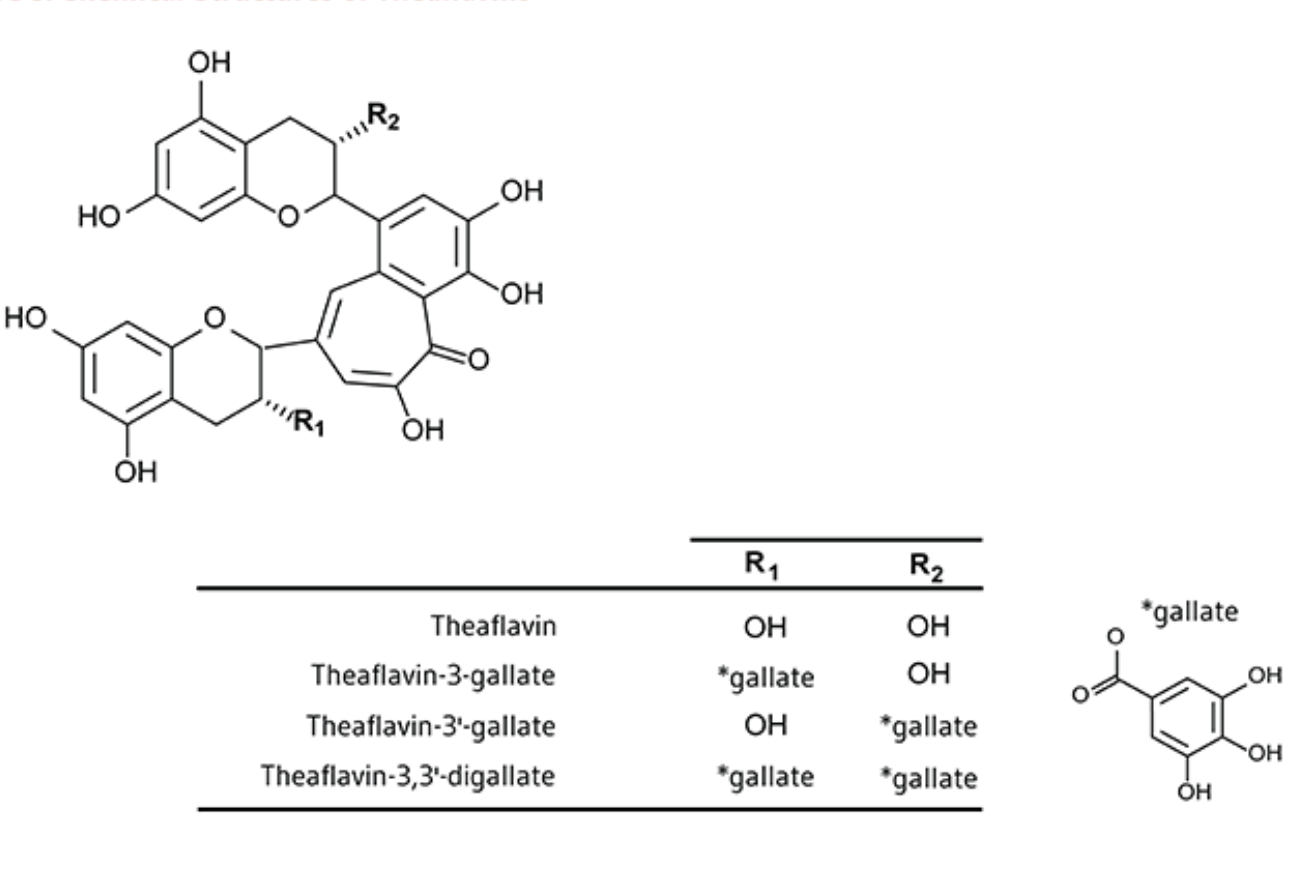

R1
R2
Theaflavin OH OH
Theaflavin-3-gallate *gallate OH
Theaflavin-3'-gallate OH *gallate
Theaflavin-3,3'-digallate *gallate *gallate
*gallate

Figure 4. Chemical Structures of Anthocyanidins

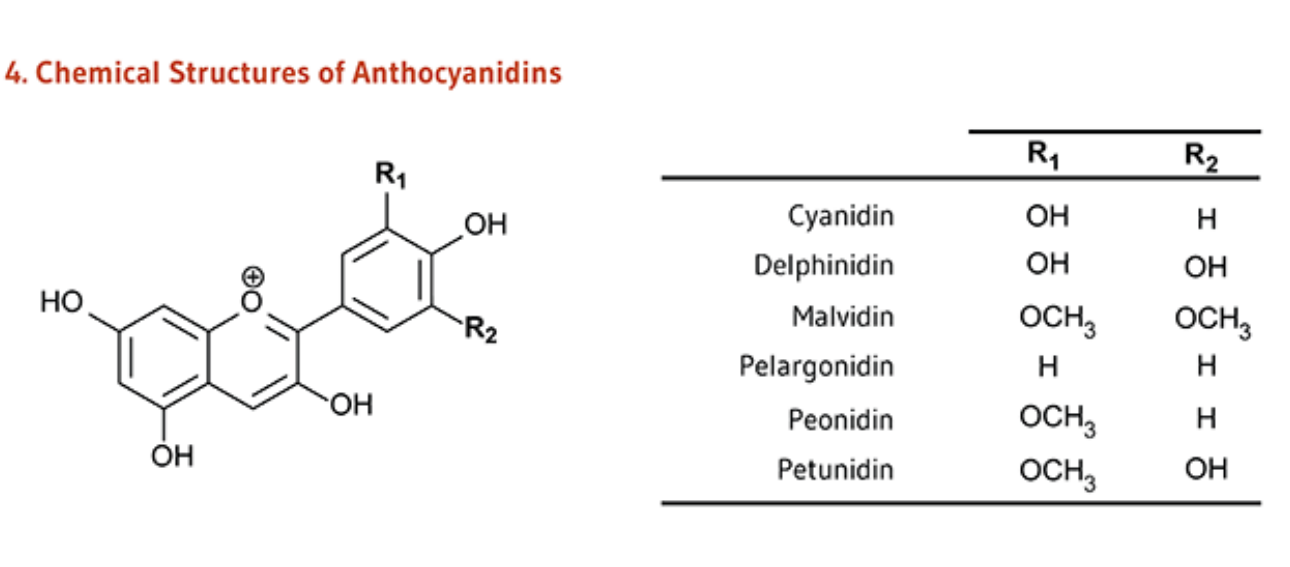


Figure 5. Chemical Structures of Flavonols

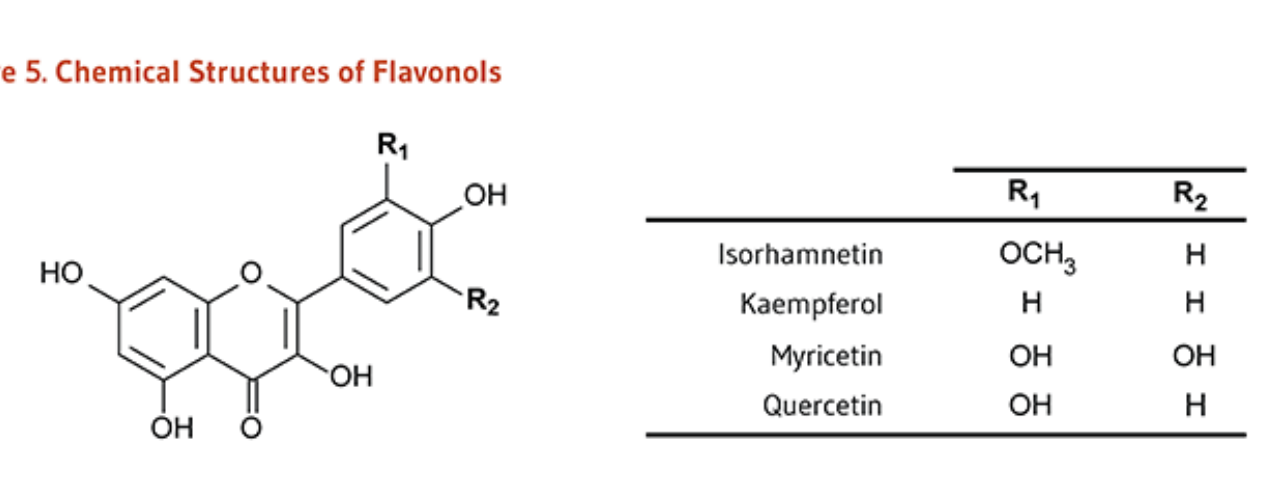


Figure 6. Chemical Structures of Flavones

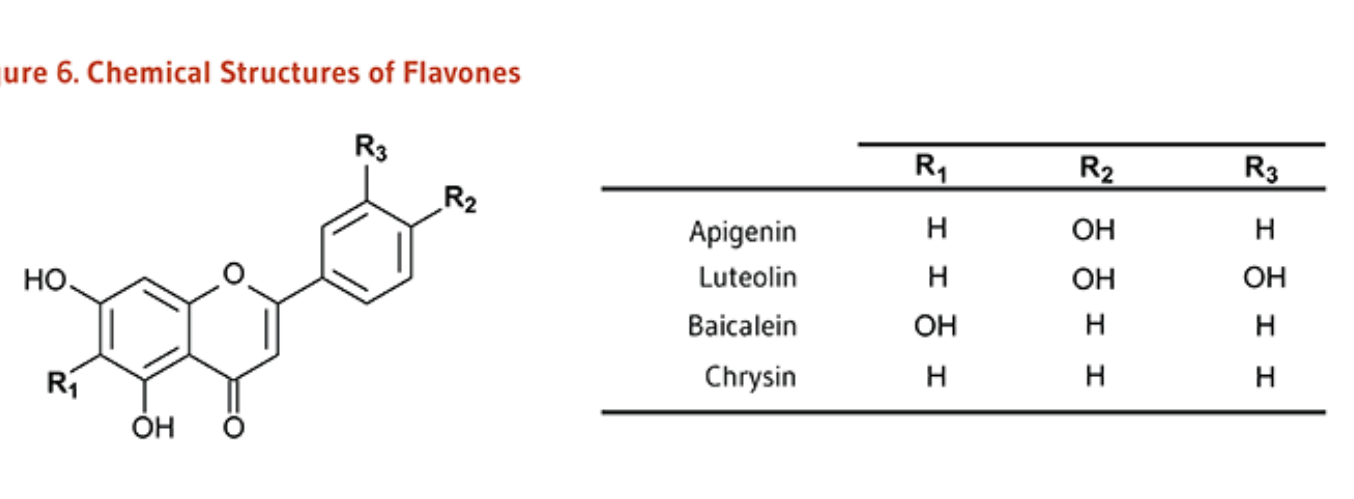


Figure 7. Chemical Structures of Flavanones

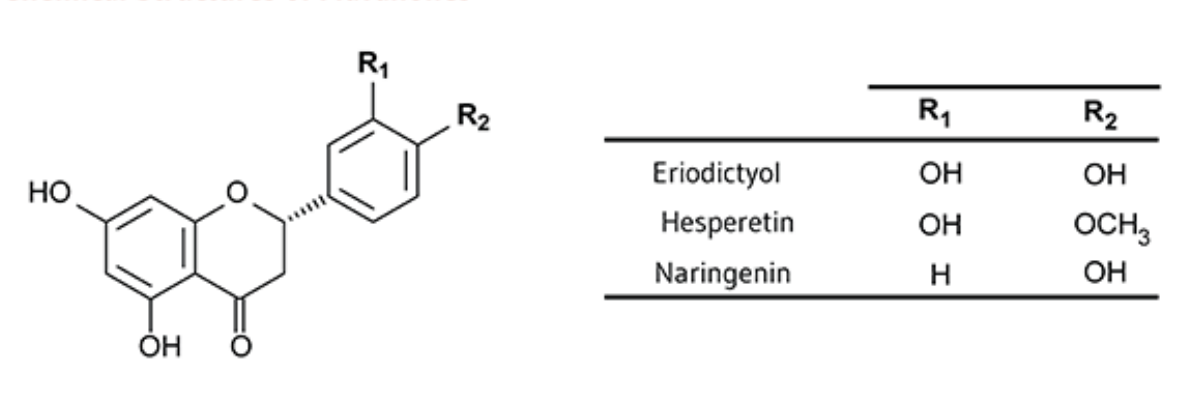


Figure 8. Chemical Structures of Isoflavones

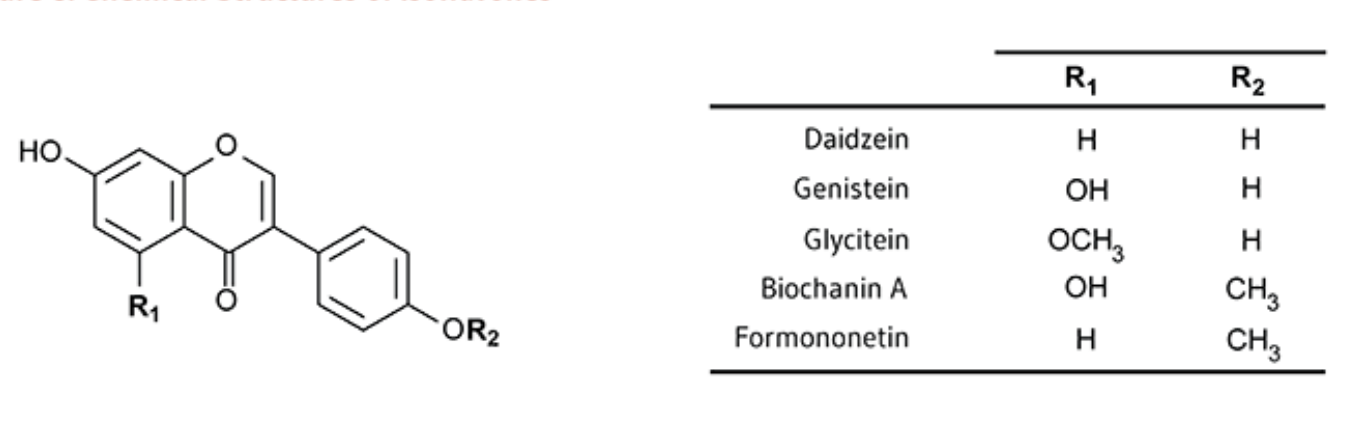
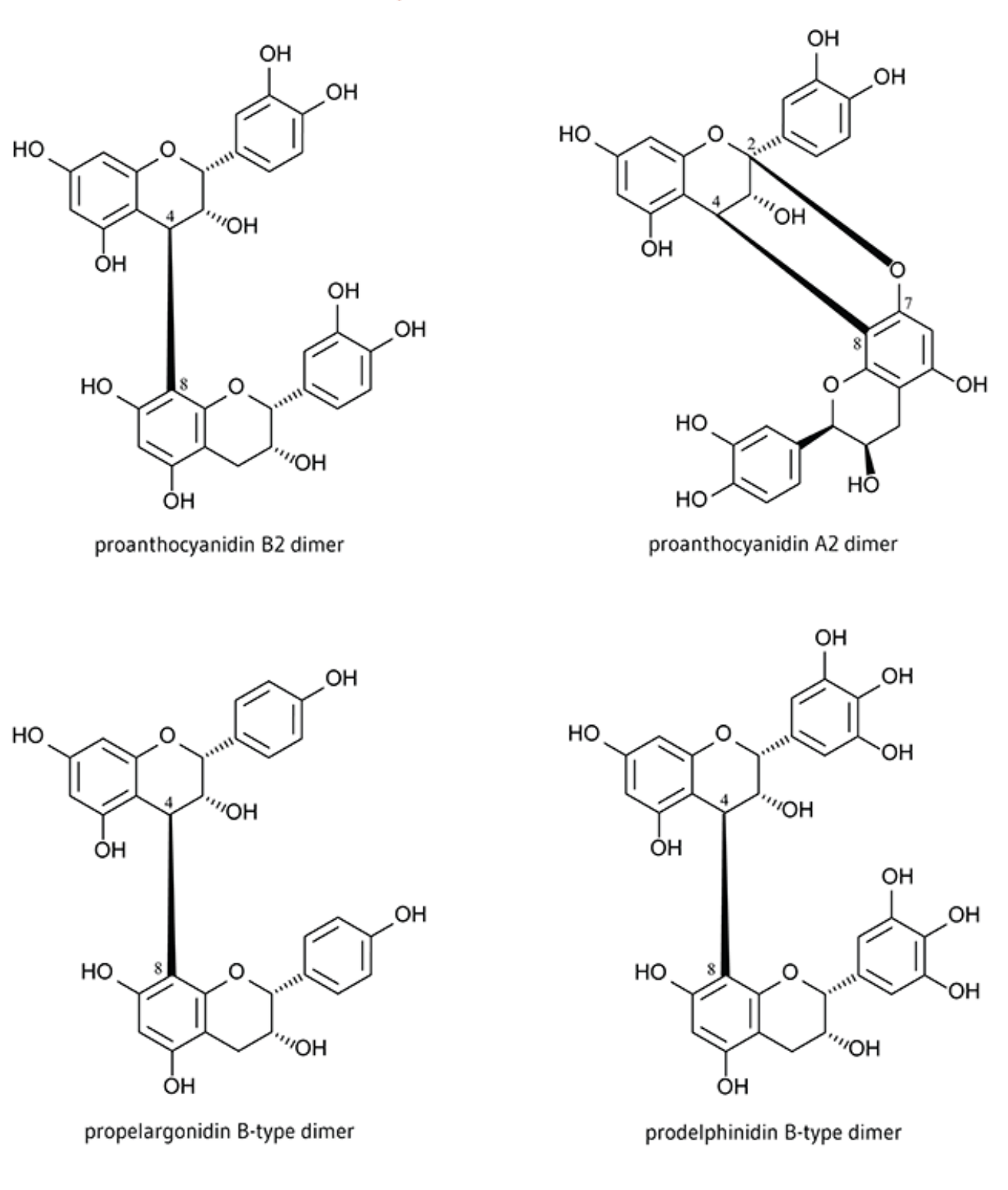


Figure 9. Chemical Structures of Proanthocyanidin Dimers


proanthocyanidin B2 dimer
proanthocyanidin A2 dimer
propelargonidin B-type dimer
prodelphinidin B-type dimer

Metabolism and Bioavailability

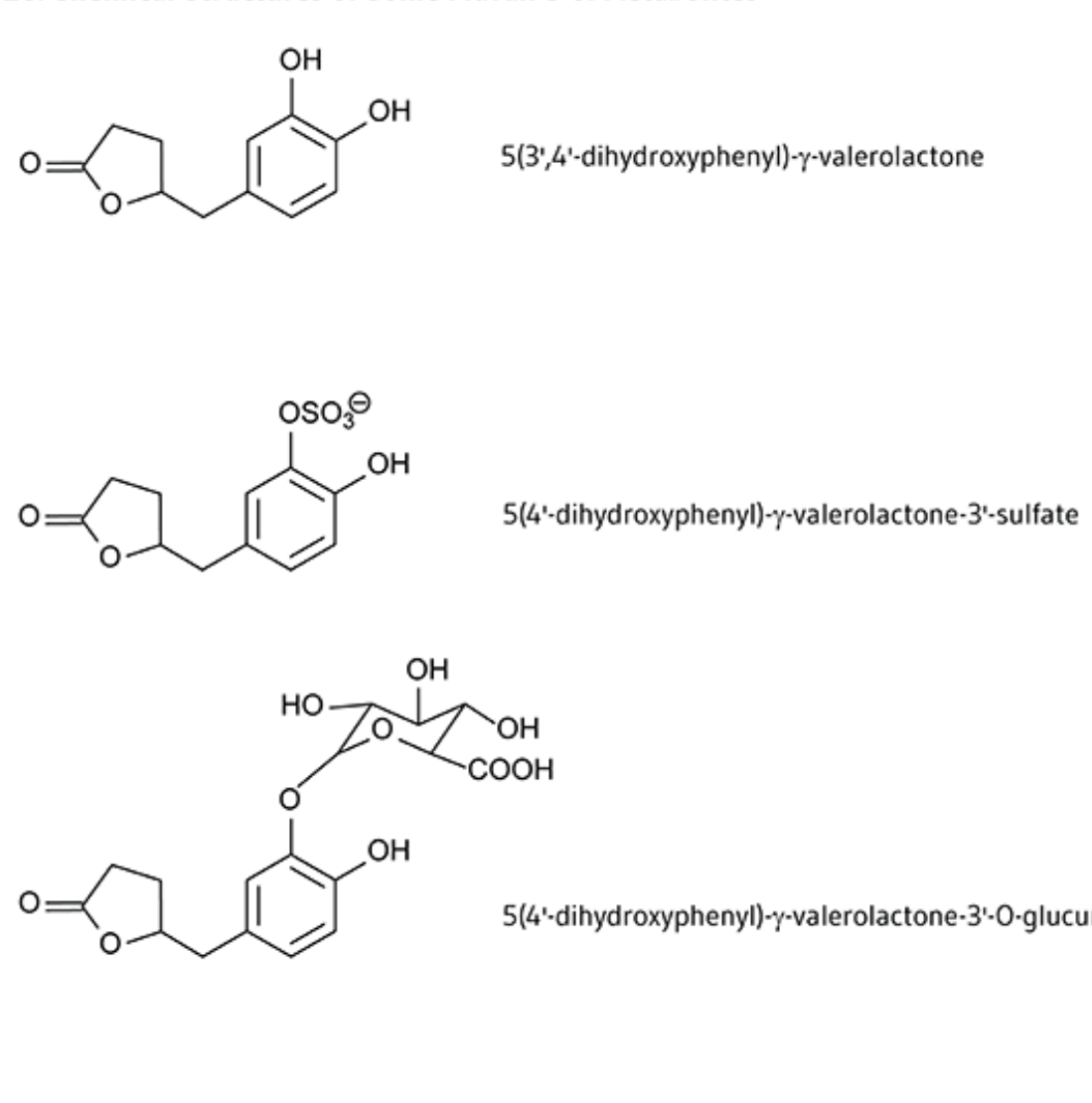
The amount of flavonoids present in ingested food has little importance unless dietary flavonoids are absorbed and become available to target tissues within the body. During and after intestinal absorption, flavonoids are rapidly and extensively metabolized in intestinal and liver cells such that they are likely to appear as metabolites (e.g., phase II metabolites) in the bloodstream and urine (4). Additionally, the biological activities of flavonoid metabolites are likely to be different from those of their parent compounds (5). Some of the factors influencing the metabolic fate and bioavailability of dietary flavonoids are mentioned below.

Chemical structure of flavonoids

Most flavonoids occur in edible plants and foods as β-glycosides, i.e., bound to one or more sugar molecules (6). Exceptions include flavan-3-ols (catechins and proanthocyanidins) and fermented soy-based products that are exposed to microbial β-glucosidases, which catalyze the release of sugar molecules from glycosylated isoflavones (7). Even after food processing and cooking, most flavonoid glycosides reach the small intestine intact. Only flavonoid aglycones (not bound to a sugar molecule) and a few flavonoid glucosides (bound to glucose) are easily absorbed in the small intestine (8). Glycosylated flavonoids might be able to penetrate the mucus layer of the intestine and be deglycosylated on the cell surface before absorption. Those that cannot be deglycosylated in the small intestine may be hydrolyzed by bacterial enzymes in the colon (7). Nevertheless, colonic bacteria might remove sugar moieties and rapidly degrade aglycone flavonoids, thus limiting their absorption in the colon (9).

In contrast to monomeric flavan-3-ols (catechins), the polymeric nature of proanthocyanidins likely prevents their intestinal absorption. Flavan-3-ol monomers and procyanidins are transformed by the intestinal microbiota to 5-(hydroxyphenyl)-γ-valerolactones which appear in the circulatory system and are excreted in urine as sulfate and glucuronide metabolites (**Figure 10**). Valerolactones may be further degraded by the colonic microbiota to smaller phenolic acids and aromatic compounds. The colonic microbiota also metabolize the gallate esters of flavonoids, generating gallate, which is further catabolized to pyrogallol. Microbe-derived flavonoid metabolites are readily absorbed into the circulatory system and excreted in both free forms and as phase II metabolites in urine (9).

Figure 10. Chemical Structures of Some Flavan-3-ol Metabolites


5(3',4'-dihydroxyphenyl)-γ-valerolactone
5(4'-dihydroxyphenyl)-γ-valerolactone-3'-sulfate
5(4'-dihydroxyphenyl)-γ-valerolactone-3'-O-glucuronide

Interactions with food matrix

The presence of macronutrients in food influences the bioavailability of co-ingested flavonoids (reviewed in 8, 10, 11). The binding affinity and potential (non-) covalent interactions of flavonoids with food proteins, carbohydrates, and fats are directly associated with the physicochemical properties of flavonoids (reviewed in 8). Proteins in milk might reduce the absorption of polyphenols from cocoa or black tea. The presence of milk proteins bound to flavonoids was shown to weaken the flavonoid antioxidant capacity *in vitro* (12), and milk consumption has been shown to blunt the vascular benefits of tea flavonoids in healthy volunteers (13). Some carbohydrate-rich foods may increase the deglycosylation and absorption of flavonoids by stimulating gastrointestinal motility, mucosal blood flow, and colonic fermentation. Conversely, dietary flavonoids have been shown to interfere with carbohydrate digestion and absorption (see Biological Activities).

Composition of gut microbiota

In the large intestine, gut microbial enzymes transform flavonoids through deglycosylation, ring fission, dehydroxylation, demethylation, etc. into metabolites that can then be absorbed or excreted (9, 14). The diversity and activity of colonic bacteria, which are partly dependent on a person's dietary habits, will determine which metabolites can be produced from ingested flavonoids (15, 16). The composition of the colonic microbiota can therefore affect the metabolic fate and bioavailability of dietary flavonoids (17).

The detoxification pathway

Flavonoids are recognized as xenobiotics by the body such that they undergo extensive modifications first in the intestinal mucosa and then in the liver.

Phase II enzymes

Depending on their structural characteristics, flavonoids can be rapidly transformed by phase II detoxification enzymes to form methylated, glucuronidated, and/or sulfated metabolites (2). This metabolic pathway increases the solubility of phenolic aglycones and facilitates their excretion in the bile and urine (11). Free (unconjugated) aglycones are generally absent from the bloodstream, with the possible exception of trace levels of catechins (17). Catechol-*O*-methyltransferase (COMT) is the detoxifying enzyme responsible for the methylation of the hydroxyl groups of flavonoids, producing *O*-methylated flavonoids. A single nucleotide polymorphism (SNP) in the gene for COMT — known as SNP rs4680 G>A — causes a valine-to-methionine substitution in the sequence of the enzyme. Individuals with the A/A genotype have a form of the enzyme that is three- to four-fold less active than the wild-type variant in G/G genotype carriers (18). It has been suggested that subjects who are less efficient at eliminating green tea flavonoids may be more likely to benefit from their consumption (19).

Efflux transporters

Flavonoid conjugates are excreted via the action of efflux transporters from the ATP-binding cassette (ABC) family, including P-glycoprotein, MRPs (multidrug resistance proteins), or BCRPs (breast cancer-resistant proteins). Depending on their physicochemical properties, some flavonoids may interfere with the activity of ABC transporters (20). This implies that flavonoids can affect their own bioavailability, as well as that of other substrates of these transporters (e.g., pharmacological drugs) (see Drug interactions).

Binding to plasma proteins

Flavonoid bioavailability may be inversely related to their binding affinity to plasma proteins (21). Greater binding affinity to plasma proteins (and thus, possibly, lower flavonoid bioavailability) has been linked to structural characteristics, such as methylation and galloylation. On the contrary, glycosylation reduced binding affinity to plasma proteins, suggesting that aglycones might have a limited bioavailability compared to glycosylated flavonoids. While glucuronidation is thought to facilitate the excretion of flavonoids from the body, glucuronides show little affinity to plasma proteins and might thus be able to diffuse to target tissues where deglucuronidation can take place (8).

Summary

In general, the bioavailability of flavonoids is low due to limited absorption, extensive metabolism, and rapid excretion. Isoflavones are thought to be the most bioavailable of all flavonoid subclasses, while anthocyanins and galloylated catechins are very poorly absorbed (8, 22). Yet, given the wide variability in structures within subclasses, it is difficult to generalize the absorbability and bioavailability of flavonoids based only on their structural classification. In addition, when evaluating the data from flavonoid research in cultured cells, it is important to consider whether the flavonoid concentrations and metabolites used are physiologically relevant (23). In humans, peak plasma concentrations of soy isoflavones and citrus flavanones have not been found to exceed 10 micromoles/liter (μM) after oral consumption. Peak plasma concentrations measured after the consumption of anthocyanins, flavan-3-ols, and flavonols (including those from tea) are generally lower than 1 μM (2). A recent quantitative analysis of 88 polyphenolic metabolites (not limited to flavonoids) identified in human blood and urine found median peak concentrations of 0.9 μM and 3.2 μM after food intake and oral supplementation, respectively (4).

Biological Activities

Direct antioxidant activity

Flavonoids are effective scavengers of free radicals in the test tube (*in vitro*) (24, 25). However, even with very high flavonoid intakes, plasma and intracellular flavonoid concentrations in humans are likely to be 100 to 1,000 times lower than concentrations of other antioxidants, such as ascorbate (vitamin C), uric acid, and glutathione. Moreover, most circulating flavonoids are actually flavonoid metabolites, some of which have lower antioxidant activity than the parent flavonoid (5). For these reasons, the relative contribution of dietary flavonoids to plasma and tissue antioxidant function *in vivo* is likely to be very small or negligible (26-28).

Metal chelation

Metal ions, such as iron and copper, can catalyze the production of free radicals. The ability of flavonoids to chelate (bind) metal ions appears to contribute to their antioxidant activity *in vitro* (29, 30). In living organisms, most iron and copper are bound to proteins, limiting their participation in reactions that produce free radicals. Although the metal-chelating activities of flavonoids may be beneficial in pathological conditions of iron or copper excess, it is not known whether flavonoids or their metabolites function as effective metal chelators *in vivo* (26).

Effects on cell-signaling pathways

Cells are capable of responding to a variety of different stresses or signals by increasing or decreasing the availability of specific proteins. The complex cascades of events that lead to changes in the expression of specific genes are known as cell-signaling pathways or signal transduction pathways. These pathways regulate numerous cell processes, such as proliferation, differentiation, inflammatory responses, apoptosis (programmed cell death), and survival. Although it was initially hypothesized that the biological effects of flavonoids would be related to their antioxidant activity, available evidence from cell culture experiments suggests that many of the effects of flavonoids, including antiinflammatory, antidiabetic, anticancer, and neuroprotective activities, are related to their ability to modulate cell-signaling pathways (27). Intracellular concentrations of flavonoids required to affect cellular signaling are considerably lower than those required to affect cellular antioxidant capacity. Flavonoid metabolites may retain their ability to interact with cell-signaling proteins even if their antioxidant activity is diminished (31, 32).

Effective signal transduction requires proteins known as kinases that catalyze the phosphorylation of target proteins, which become either activated or inhibited. Cascades involving specific phosphorylations or dephosphorylations of signal transduction proteins ultimately affect the activity of transcription factors — proteins that bind to specific response elements on DNA and promote or prevent the transcription of target genes. Results of numerous studies in cell culture suggest that flavonoids may affect chronic disease by selectively inhibiting kinases (27, 33). Cell growth and proliferation are also regulated by growth factors that initiate cell-signaling cascades by binding to specific receptors in cell membranes. Flavonoids may alter growth factor signaling by inhibiting receptor phosphorylation or blocking receptor binding by growth factors (34).

Each flavonoid subclass contains many types of chemicals with varying biological activities (and potential health benefits) such that the activity of a specific flavonoid cannot easily be generalized. Some examples of major biological activities of flavonoids are highlighted below.

Biological activities related to the prevention of cardiovascular disease

Flavonoids have been shown to (1) reduce inflammation by suppressing the expression of pro-inflammatory mediators (35-37); (2) down-regulate the expression of vascular cell adhesion molecules, which contribute to the recruitment of inflammatory white blood cells from the blood to the arterial wall (38, 39); (3) increase the production of nitric oxide (NO) by endothelial nitric oxide synthase (eNOS), thus improving vascular endothelial function (40); (4) inhibit angiotensin-converting enzyme, thus inducing vascular relaxation (41); (5) inhibit platelet aggregation (42); and (6) oppose smooth muscle cell proliferation and migration occurring during atherogenesis (43).

Biological activities related to the prevention of diabetes

Flavonoids have been found to interfere with the digestion, absorption, and metabolism of carbohydrates (reviewed in 44). Each subclass of flavonoids has also demonstrated anti-diabetic properties, including (1) improving insulin secretion and viability of pancreatic β-cells under glucotoxic or pro-inflammatory conditions, (2) increasing insulin-stimulated glucose uptake by target cells, (3) protecting muscle cells against fatty acid-induced insulin resistance, and (4) reducing hyperglycemia and improving glucose tolerance in animal models of obesity and/or type 2 diabetes mellitus (45).

Biological activities related to the prevention of cancer

Flavonoids have been found to (1) scavenge free radicals that can damage macromolecules, including DNA (46, 47); (2) interfere with biotransformation enzymes and efflux transporters, possibly preventing the activation of procarcinogenic chemicals and promoting their excretion from the body (48, 49); (3) regulate proliferation, DNA repair, or activation of pathways leading to apoptosis (programmed cell death) in case of irreversible DNA damage (50); and (4) inhibit tumor invasion and angiogenesis (51, 52).

Biological activities related to neuroprotection and cognitive function

Flavonoids are thought to (1) promote neurogenesis, synaptic growth, and neuron survival in the learning and memory-related brain regions (e.g., hippocampus) by stimulating the production of neurotrophins like BDNF; (2) protect hippocampal cells and striatal dopaminergic cells from cytotoxic molecules (pro-inflammatory mediators and ROS) released by abnormally activated microglia and hypertrophic astrocytes in neurodegenerative disorders; (3) reduce neuroinflammation by inhibiting the generation of pro-inflammatory cytokines, lipid mediators, and reactive oxygen species by astrocytes and microglial cells; (4) stimulate the production of nitric oxide (NO), which improves endothelial function, increases cerebral blood flow, and protects artery walls against the buildup of atherosclerotic plaques (reviewed in 53, 54).

Disease Prevention

Cardiovascular disease

Several prospective cohort studies conducted in the US and Europe have examined the relationship between some measure of dietary flavonoid intake and cardiovascular disease (CVD) or mortality. A recent meta-analysis of 14 prospective studies published between 1996 and 2012 reported that higher intakes in each flavonoid subclass were significantly associated with a reduced risk of cardiovascular events (55). Top versus bottom quantiles of intake for each of the flavonoid subclasses were associated with an approximate 10% reduction in the risk of CVD. Another meta-analysis of eight prospective studies found a 14% reduced risk of stroke with the highest versus lowest quintile of flavonol intakes (56). However, several serious limitations highlighted in a recent publication by Jacques et al. suggested caution when interpreting these results (57). In particular, most of the prospective studies in these meta-analyses did not include all flavonoid subclasses nor calculate intakes using the latest and more complete versions of the USDA databases for the flavonoid content of foods (58-60). Another major concern is the lack of adjustment regarding the overall quality of the diet. Consumers with higher flavonoid intakes are likely to have a greater consumption of fruit and vegetables and overall healthier diets than those with poor flavonoid intakes. Additionally, none of the studies excluded potential bias due to constituents of flavonoid-rich foods that are known to either lower (e.g., other phytochemicals, vitamins, dietary fiber) or increase (e.g., sodium, saturated fat) the risk of cardiovascular events (discussed in 57).

In the Framingham Offspring Cohort study that followed 2,880 adults for a mean of 14.9 years, consumption of all flavonoid subclasses except flavones and flavanones was inversely associated with CVD (57). Yet, adjusting for confounding factors, including fruit and vegetable intake and overall diet quality, attenuated these relationships such that they were no longer statistically significant. An analysis of a larger prospective study of the EPIC-Norfolk cohort (24,885 participants) that considered confounding by many dietary factors (vitamin C, dietary fiber, fat, saturated fat, potassium, sodium, and alcohol) found no significant association between flavan-3-ol intake and CVD-related or all-cause mortality (61).

A number of large prospective studies and small-scale, randomized controlled trials have investigated the effects of flavonoids on established biomarkers of CVD, including those involved in oxidative stress, inflammation, abnormal blood lipid profile, endothelial dysfunction, and hypertension; some of these studies are highlighted below.

Biochemical markers of cardiovascular disease

In a cross-sectional analysis of the Framingham Offspring Cohort study, the highest versus lowest intake of anthocyanins (≤3.5 mg/day versus ≥23.5 mg/day) was associated with lower concentrations of acute-phase reactant proteins (-100%), pro-inflammatory cytokines (-75%), and markers of oxidative stress (-52%), even after adjustment for confounding variables (62). Interestingly, a food-based analysis revealed that intakes of foods rich in anthocyanins, e.g., apples, red wine, and strawberries, were also inversely associated with an overall inflammation score based on 12 different biomarkers. Higher intakes of polymeric flavan-3-ols (i.e., theaflavins, thearubigins, and proanthocyanidins) were correlated with lower concentrations of pro-inflammatory cytokines and biomarkers of oxidative stress. Intake levels of total flavonoids and flavan-3-ol monomers (i.e., catechins) were inversely associated with concentrations of the biomarkers of oxidative stress. Although tea is a major source of flavan-3-ols, tea consumption was not correlated with the composite inflammation score or any components of this score in this study (62).

Cocoa is another source of flavan-3-ols, in particular (-)-epicatechin and procyanidins, that may provide cardiovascular benefits (63). Indeed, a recent randomized, double-blind, placebo-controlled study in 100 healthy adults (ages, 35-60 years) suggested that short-term benefits of cocoa flavan-3-ol consumption on cardiovascular health, including improvements in lipoprotein profile (i.e., higher HDL-cholesterol and lower total and LDL-cholesterol) and blood pressure, could be extrapolated to predict a 20%-30% reduced 10-year risk of CVD and CVD-related mortality (64).

An increasing number of trials in which participants were fed with berries (65-67) or juices (68) rich in anthocyanins or with purified anthocyanins (69) also reported reduced levels of inflammatory markers and/or improved antioxidant status, decreased LDL-cholesterol, improved insulin sensitivity, and lowered blood pressure (reviewed in 70). In a randomized, double-blind, placebo-controlled study in 150 individuals with hypercholesterolemia, supplementation with a purified anthocyanin mixture (320 mg/day) for 24 weeks reduced circulating markers of inflammation, including C-reactive protein (CRP), interleukin-1β (IL-1β), and soluble vascular adhesion molecule-1 (sVCAM-1) (71). Supplementation of dyslipidemic patients for 12 or 24 weeks with a mixture of 17 anthocyanins improved cholesterol clearance via the HDL-mediated reverse cholesterol transport from extra-hepatic tissues back to the liver and lowered LDL-cholesterol compared to a placebo in two randomized controlled trials (72, 73). However, a 12-week, randomized, double-blind, placebo-controlled study in 52 healthy postmenopausal women found that daily consumption of 500 mg of elderberry anthocyanins (as cyanidin-3-glucoside) had no effect on inflammation markers, markers of vascular health, lipid profile, and glycemia; all of these measures were in normal range of concentrations at baseline (74). Whether exposure to high-dose anthocyanins could lower the risk of CVD in subjects with established CVD risk factors and/or help maintain cardiovascular health in apparently healthy individuals remains to be confirmed.

Endothelial dysfunction

The vascular endothelial cells that line the inner surface of all blood vessels synthesize an enzyme, endothelial nitric oxide synthase (eNOS), whose function is essential to normal vascular physiology. Specifically, eNOS produces nitric oxide (NO), a compound that regulates vascular tone and blood flow by promoting the relaxation (vasodilation) of all types of blood vessels, including arteries (75). NO also regulates vascular homeostasis and protects the integrity of the endothelium by inhibiting vascular inflammation, leukocyte adhesion, platelet adhesion and aggregation, and proliferation of vascular smooth muscle cells (76). In the presence of cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, hyperglycemia), early alterations in the structure and function of the vascular endothelium are associated with the loss of normal NO-mediated endothelium-dependent vasodilation. Endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities and is considered to be an early step in the development of atherosclerosis. Measures of brachial flow-mediated dilation (FMD), a surrogate marker of endothelial function, have been found to be inversely associated with risk of future cardiovascular events (77).

Preclinical studies have demonstrated the benefits of berry fruits, extracts, or purified anthocyanins on vascular function. Anthocyanin supplementation to diabetic mice was found to improve diabetes-induced vascular dysfunction by promoting NO-mediated endothelium-dependent vasodilation through the upregulation of adipocyte-derived adiponectin (78). Supplementation with purified anthocyanins (320 mg/day for 12 weeks) also increased serum adiponectin concentrations and improved FMD in 58 individuals with type 2 diabetes (78). In a randomized trial of 150 participants with hypercholesterolemia, supplemental anthocyanins increased FMD values by 28.4% compared to 2.2% in the placebo group (79).

Several small-scale, intervention studies have also examined the effect of flavan-3-ol-rich food and beverages, including tea, red wine, purple grape juice, cocoa, and chocolate, on endothelium-dependent vasodilation. A meta-analysis of nine intervention studies in a total of 213 participants estimated that the acute ingestion of 2 to 3 cups of tea (500 mL) — containing about 248 mg of flavonoids in green tea and 415 mg in black tea — significantly increased brachial FMD (see also the article on Tea) (80). Another meta-analysis of 18 randomized controlled studies found that acute (2 h post-ingestion) and chronic (≤18 months) consumption of flavan-3-ol-rich cocoa beverages and chocolate bars significantly increased FMD in participants (81). A small 15-day, cross-over intervention study in hypertensive individuals with endothelial dysfunction found that 100 g/day of flavan-3-ol-rich dark chocolate, but not 90 g/day of flavan-3-ol-free white chocolate, could restore FMD values almost to normal levels (82). Also, using a similar protocol, the authors showed that dark chocolate intake blunted acute endothelial dysfunction-induced by a glucose load challenge in 12 healthy volunteers (83). Other benefits of dark chocolate consumption included reductions in arterial stiffness (measured through pulse wave analysis) and serum concentrations of markers of oxidative stress and vasoconstriction (8-isoprostaglandin F2α and endothelin-1). A randomized controlled trial in overweight and obese participants also reported that the daily consumption of a high-flavan-3-ol cocoa drink (902 mg/day of flavan-3-ols), but not that of a cocoa drink low in flavan-3-ols (38 mg/day), resulted in a sustained increase in FMD during the 12-week study (84). A more recent four-week, randomized, double-blind, cross-over, controlled study in healthy overweight or obese adults found that the consumption of 22 g/day of natural cocoa (in the form of dark chocolate bar and cocoa drink; 814 mg/day of flavan-3-ols) increased arterial diameter and blood flow and lowered peripheral arterial stiffness, but there was no change in FMD (85). Another recent clinical trial found improvements in endothelium-dependent vasodilation in response to acute consumption of one bar (40 g) of dark chocolate (containing 10.8 mg of (+)-catechins and 36 mg of (-)-epicatechins) and daily consumption of two bars (80 g) for up to four weeks in 20 individuals with chronic heart failure (86). Oral administration of pure flavan-3-ol (-)-epicatechin to healthy volunteers showed NO-dependent vasodilatory effects similar to those observed following flavan-3-ol-rich cocoa ingestion (87). Administration of (-)-epicatechin also improved acetylcholine-induced endothelial-dependent vasodilation of thoracic aorta rings from rats with salt-induced hypertension (88).

Endothelial nitric oxide production also inhibits the adhesion and aggregation of platelets, one of the first steps in atherosclerosis and blood clot formation (76). A number of clinical trials that examined the potential for high flavonoid intakes to decrease various measures of platelet function outside of the body (*ex vivo*) have reported mixed results. A recent systematic review of these intervention studies suggested that consumption of flavan-3-ol-rich cocoa and grape seed extract was generally found to improve platelet function by inhibiting platelet adhesion, activation, and aggregation (89). Interestingly, in a cross-over, controlled study, the acute consumption of a flavan-3-ol-rich cocoa beverage (897 mg of total (-)-EC and procyanidins) exhibited additive anti-platelet effects to aspirin (81 mg) in healthy volunteers (90). In contrast, the results of interventions using apigenin-rich soup, quercetin-rich supplements or onion soups, isoflavone-rich soy protein isolates, black tea, wines, berries, or grape juices have given inconsistent results (reviewed in 89).

Hypertension

A meta-analysis of 20 short-term, randomized controlled trials, including a total of 856 mainly healthy participants, found that consumption of flavan-3-ol-rich dark chocolate and cocoa products significantly reduced systolic blood pressure by 2.77 mm Hg and diastolic blood pressure by 2.20 mm Hg. However, heterogeneity across studies was high, and risk of bias was significant (91). A greater blood pressure-reducing effect was observed in a subanalysis of studies using flavan-3-ol-free rather than flavan-3-ol-low control groups (91). Another meta-analysis of 22 trials (highly heterogeneous) found reductions in diastolic blood pressure (-1.60 mm Hg) and mean arterial pressure (-1.64 mm Hg) with chocolate or cocoa intake but no change in systolic blood pressure (81). Additionally, green tea flavan-3-ols have been shown to lower blood pressure especially in (pre-) hypertensive subjects. A pooled analysis of 13 randomized controlled trials in 1,040 subjects found a 2.05 mm Hg reduction in systolic blood pressure and a 1.71 mm Hg reduction in diastolic blood pressure with green tea consumption for at least three weeks (92). The inhibition of angiotensin-converting enzyme (ACE), a key regulator of arterial blood pressure, may partly explain how flavan-3-ol-rich food and beverages might exert blood pressure-lowering effects (93).

Some intervention trials have also examined the effect of the flavonol quercetin on blood pressure in human subjects. In a randomized, double-blind, cross-over, placebo-controlled trial in 96 participants diagnosed with metabolic disorders, supplementation with 150 mg/day of quercetin aglycone significantly reduced systolic blood pressure by 2.6 mm Hg without affecting diastolic blood pressure and other cardiometabolic markers (94). Similar results were found with 730 mg/day of quercetin in hypertensive individuals (95) and with 500 mg/day of quercetin in women with type 2 diabetes mellitus (96). In a recent six-week, cross-over, randomized, double-blind, placebo-controlled trial, daily ingestion of 162 mg of quercetin decreased 24 h-ambulatory blood pressure — but not systolic blood pressure in the resting state — in hypertensive but not in pre-hypertensive participants (97). There was no change in biomarkers of lipid metabolism, inflammation, oxidative stress, or endothelial function, including total, HDL-, LDL-cholesterol, serum CRP, soluble adhesion molecules, plasma oxidized LDL, urinary 8-isoprostaglandin F2α, serum endothelin-1, serum ACE, and plasma endogenous NOS inhibitor.

Additional trials may help establish whether the blood pressure-lowering effect of some flavonoids could be translated into long-term benefits for cardiovascular health.

Type 2 diabetes mellitus

The association between flavonoid consumption and risk for type 2 diabetes mellitus has been examined in a recent European, multicenter, nested case-control study — the "EPIC-InterAct" project — that included 16,835 diabetes-free participants and 12,043 diabetics. In this study, participants in the highest quintile of total flavonoid intake (>608.1 mg/day) had a 10% lower risk of diabetes than those in the lowest quintile (<178.2 mg/day) (98). Specifically, the risk of diabetes was inversely correlated with the intake of flavan-3-ols (monomers and dimers only) and flavonols (98, 99). Recent meta-analyses of randomized controlled trials have examined the possible health effects of green tea flavan-3-ol monomers (catechins) on glucose metabolism and have provided conflicting results. A meta-analysis of seven trials in pre-diabetic and diabetic patients found no effect of green tea or green tea extracts on fasting plasma glucose, fasting serum insulin, or measures of glycemic control (glycated hemoglobin, HbA1c) and insulin sensitivity (HOMA-IR) (100). Conversely, another meta-analysis of 17 trials in pre-diabetic, diabetic, or overweight/obese subjects found that administration of green tea extracts for 4 to 16 weeks improved fasting plasma glucose and HbA1c level (101). The effect on fasting glucose was observed only with high doses of catechins (≥457 mg/day) and when the confounding effect of caffeine was removed. Finally, a third meta-analysis of 25 trials found that ingestion of green tea extracts for at least two weeks could lower fasting blood glucose in both the presence or absence of caffeine (102).

Dark chocolate is another good source of flavan-3-ols such that the effects of cocoa flavan-3-ols have been examined in individuals at-risk or with established type 2 diabetes. In a 15-day, cross-over, randomized controlled study, the daily consumption of 100 g of dark chocolate bars containing 110.9 mg of (-)-EC and 36.1 mg of (+)-C significantly improved measures of pancreatic β-cell function and insulin sensitivity, along with cardiometabolic markers in glucose-intolerant and hypertensive subjects (103). Daily supplementation with flavonoid-enriched chocolate containing 850 mg of flavan-3-ols and 100 mg of isoflavones for one year significantly improved insulin sensitivity and reduced a predicted risk of coronary heart disease (CHD) at 10 years in 93 postmenopausal women treated for type 2 diabetes (104).

The EPIC-InterAct study did not find any association between dietary anthocyanin intake and risk of diabetes (98, 99). Yet, a 10-fold increase in anthocyanin consumption was correlated with a 15% lower risk of diabetes in the pooled analysis of three large US prospective cohorts (120,003 participants) (105). Of note, this pooled analysis also reported a moderately higher risk of diabetes (+6%) in individuals in the highest versus lowest quintiles of flavone and flavanone intakes. Moreover, the consumption of berries, rich in anthocyanins, has been shown to trigger favorable glycemic responses in type 2 diabetics (reviewed in 70). In recent intervention studies, anthocyanins demonstrated beneficial effects on metabolic abnormalities in patients at-risk or diagnosed with diabetes. In an eight-week, randomized, double-blind, placebo-controlled trial in 38 healthy overweight and obese subjects, the consumption of 2 g/day of grape polyphenols rich in proanthocyanidins and anthocyanins prevented increases in oxidative stress and insulin resistance induced by a six-day, high-fructose challenge (106). Another six-week randomized trial in individuals with diabetes showed that daily supplementation with Cornelian cherry (*Cornus mas*) extracts containing 600 mg of anthocyanins significantly lowered serum levels of HbA1c and triglycerides and increased serum insulin concentrations (107). The administration of 320 mg/day of anthocyanins for 24 weeks also improved serum lipid and lipoprotein profile, decreased markers of oxidative stress and inflammation, elevated antioxidant capacity, and reduced insulin resistance compared to a placebo in patients with diabetes (108). Further, supplemental anthocyanins up-regulated adiponectin expression and improved nitric oxide-mediated endothelium-dependent vasodilation within 12 weeks of treatment (see also Cardiovascular disease) (78).

These promising findings warrant additional randomized controlled trials to confirm preventive and/or therapeutic benefits of (cocoa) flavan-3-ols and anthocyanins in type 2 diabetes.

Cancer

Although various flavonoids have been found to inhibit the development of chemically-induced cancers in animal models of lung (109), oral (110), esophageal (111), gastric (112), colon (113), skin (114), prostate (115, 116), and mammary cancer (117), observational studies do not provide convincing evidence that high intakes of dietary flavonoids are associated with substantial reductions in human cancer risk (reviewed in 118). A meta-analysis of 13 case-control and 10 prospective cohort studies found little-to-no evidence to support a preventive role of dietary flavonoid intake in gastric and colorectal cancer (119). In addition, a recently published analysis of two large prospective studies (the Health Professionals Follow-up Study [HPFS] and the Nurses' Health Study [NHS]) — using the most up-to-date flavonoid food composition databases — found no association between the risk of colorectal cancer and intakes of each subclass of flavonoids or flavonoid-rich foods (tea, blueberries, oranges) (120). A meta-analysis of 19 case-control studies and 15 cohort studies found that total flavonoid intake and intakes of specific flavonoid subclasses (i.e., flavonols, flavones, flavanones) were inversely correlated with the risk of smoking-sensitive cancers of the aerodigestive tract (mouth, pharynx, larynx, esophagus, and stomach) in smokers but not in nonsmokers (121). The risk of lung cancer was not significantly associated with high flavonoid intakes (121), although an earlier meta-analysis of eight prospective studies (with substantial heterogeneity across them) suggested a protective role of flavonoids against lung cancer in smokers only (122). Further, a prospective analysis of over 45,000 postmenopausal women from the Multiethnic Cohort Study found a reduced risk of endometrial cancer with the highest intakes of total isoflavones, daidzein, and genistein (123). Additionally, limited evidence from observational studies suggests no relationship between total flavonoid intake and ovarian cancer (124-127). To date, there is little evidence that flavonoid-rich diets might protect against various cancers, but larger prospective cohort studies are needed to address the association.

Hormone-dependent cancers

Because isoflavones are phytoestrogens, it is thought that they may interfere with the synthesis and activity of endogenous hormones, eventually influencing hormone-dependent signaling pathways and protecting against breast and prostate cancers (128). A meta-analysis of 14 observational studies that examined breast cancer incidence in 369,934 women found an overall 11% reduced risk of breast cancer with the highest versus lowest intake of soy isoflavones (129). Subgroup analyses revealed a 24% lower risk of cancer in Asian but not in European or US women, and the risk was 22% lower in postmenopausal but not lower in premenopausal women. In addition to the ethnicity and menopausal status, polymorphisms for hormone receptors (130) and phase I biotransformation enzymes (131) have been found to modify the association between isoflavone intake and breast cancer. Another recent meta-analysis of 12 observational studies (six prospective cohort studies, one nested case-control study, and five case-control studies) investigated the chemopreventive effects of flavonoids (except isoflavones) (132). The results suggested that intakes of flavonols and flavones may also be inversely associated with the risk of breast cancer. Further, a pooled analysis of four case-control studies that stratified by menopausal status showed inverse associations between breast cancer and intakes of flavonols, flavones, or flavan-3-ols in postmenopausal women only. Finally, a meta-analysis of four prospective cohort studies found an overall 16% reduced risk of breast cancer recurrence in women with high versus low isoflavone intakes (129).

A meta-analysis of 13 observational studies also suggested an inverse relationship between prostate cancer risk and consumption of soy products, especially tofu (133). Yet, further analyses supported a protective role of soy food based only on case-control studies, which have inherent flaws such that associations may often be overestimated or underestimated. In a recent 12-month, multicenter, randomized, double-blind, placebo-controlled phase II clinical trial in 158 Japanese men (aged ≥50 years) with elevated risk of prostate cancer, oral isoflavone (60 mg/day) resulted in a significant decrease in prostate cancer incidence in participants aged 65 years and older (134). In this study, no changes were reported in sex hormone concentrations in blood, suggesting that isoflavones may reduce prostate cancer incidence without interfering with hormone-dependent pathways.

Additional investigations will be necessary to determine whether supplementation with specific flavonoids could benefit cancer prevention or treatment.

For more information on flavonoid-rich foods and cancer, see articles on Fruit and Vegetables, Legumes, and Tea.

Cognitive function

Inflammation, oxidative stress, and transition metal accumulation appear to play a role in the pathology of several neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease (135). Therefore, the various properties of flavonoids, including their role in protecting vascular health, could have beneficial effects on the brain, possibly in the protection against cerebrovascular disorders, cognitive impairments, and subsequent stroke and dementias. Dietary flavonoids and/or their metabolites have been shown to cross the blood-brain barrier (54) and exert preventive effects towards cognitive impairments in animal models of normal and pathological aging (53).

The cross-sectional data analysis of 2,031 participants (ages, 70-74 years) from the Hordaland Health Study in Norway indicated that, when compared to non-consumers, consumers of flavonoid-rich chocolate, tea, and wine had better global cognitive function, assessed by a battery of six cognitive tests (136). The risk of poor performance in all tests was estimated to be 60 to 74% lower in consumers of all three flavonoid-rich foods compared to non-consumers. An early prospective cohort study in 1,367 older French men and women (aged ≥65 years; free from dementia at baseline) found that those with the lowest flavonoid intakes (<11.5 mg/day) had a 50% higher risk of developing dementia over the next five years than those with higher intakes (137). In addition, those with higher dietary flavonoid intakes at baseline experienced significantly less age-related cognitive decline over a 10-year period than those with the lowest flavonoid intakes (138).

The effect of cocoa flavan-3-ols have been investigated in an eight-week, randomized, double-blind trial — the Cognitive, Cocoa, and Aging (CoCoA) study — in 90 individuals (ages, 64-82 years) with mild cognitive impairments (MCI); participants were given dairy-based cocoa drinks with either high (993 mg/day) or low (48 mg/day) levels of flavan-3-ols (139). The daily consumption of the cocoa drink high in flavan-3-ols improved some, but not all, measures of cognitive process speed and flexibility and verbal fluency compared to baseline test scores and scores following low flavan-3-ol drink consumption. A composite test score reflecting overall cognitive performance was found to be significantly greater in those given cocoa drinks high rather than low in flavan-3-ols. The study also reported reductions in cardiovascular risk markers (i.e., systolic and diastolic blood pressure, total and LDL-cholesterol, insulin resistance), and these changes were proposed to partly contribute to ameliorate cognitive performance in those who consumed the flavan-3-ol-rich cocoa drink (139). The data could be replicated in cognitively healthy older people (ages, 61-85 years), suggesting that cocoa flavan-3-ols might enhance some aspects of cognitive function during healthy aging (140). Interestingly, a two-week, randomized, double-blind, controlled study has reported an increase in blood flow velocity in the middle cerebral artery of 21 healthy subjects (mean age, 72 years) following the daily intake of a flavan-3-ol-rich cocoa drink (900 mg/day of flavan-3-ols) (141). Because cerebral blood flow is correlated with cognitive function in humans, these preliminary data suggest that cocoa flavan-3-ol consumption could exert a protective effect against dementia (54).

Yet, in other randomized controlled trials (142-144), the lack of an effect of cocoa flavan-3-ols on blood pressure, cerebral blood flow, mental fatigue, and cognitive performance in healthy young and old adults suggested that benefits may only be seen in very demanding cognitive exercises (145).

Some randomized controlled studies also reported improvements in measures of cognitive function in healthy and cognitively impaired subjects with other flavonoid subclasses, including anthocyanins (146), flavanones (147, 148), and isoflavones (149, 150). Although some flavonoids and flavonoid-rich foods may enhance cognitive function in the aging brain, it is not yet clear whether their consumption could lower the risk of cognitive impairments and dementia in humans.

For more detailed information on flavan-3-ol-rich tea and cognitive function, see the article on Tea.

Sources

Food sources

Recent data analyses of the National Health and Nutrition Examination Survey (NHANES) estimated flavonoid intakes in US adults (aged ≥19 years) average between 200 and 250 mg/day, with 80% being flavan-3-ols, 8% for flavonols, 6% for flavanones, 5% for anthocyanidins, and ≤1% for isoflavones and flavones (151, 152). The main dietary sources of flavonoids include tea, citrus fruit, citrus fruit juices, berries, red wine, apples, and legumes. Individual flavonoid intakes may vary considerably depending on whether tea, red wine, soy products, or fruit and vegetables are commonly consumed (reviewed in 2). Information on the flavonoid content of some flavonoid-rich foods is presented in **Tables 2-8**. These values should be considered approximate since a number of factors may affect the flavonoid content of foods, including agricultural practices, environmental conditions, ripening, storage, and food processing. For additional information about the flavonoid content of food, the USDA provides databases for the content of selected foods in flavonoids (60) and proanthocyanidins (58). For more information on the isoflavone content of soy foods, see the article on Soy Isoflavones or the USDA database for the isoflavone content of selected foods (59).

Table 2. Anthocyanidin Content of Anthocyanidin-rich Foods (mg/100 g or 100 mL*)

	Anthocyanidins					
Food	**Cyanidin**	**Delphinidin**	**Malvidin**	**Pelargonidin**	**Peonidin**	**Petunidin**
Blackberries, raw	100	0	0	<1	<1	0
Blood orange juice	5.5	<1	-	-	<1	-
Blueberries, raw	8.5	35.4	67.6	0	20.3	31.5
Currants, black, raw	62.5	89.6	-	1.2	<1	3.9
Elderberries, raw	485.3	0	-	<1	-	0
Grapes, red	1.2	2.3	39	<1	3.6	2
Onions, red, raw	3.2	4.3	-	<1	2.1	-
Plums, raw	5.6	0	0	0	<1	0
Radishes, raw	0	0	0	63.1	0	0
Raspberries, raw	45.8	1.3	<1	1	<1	<1
Red cabbage, raw	209.8	<1	-	<1	-	-
Strawberries, raw	1.7	<1	<1	24.9	<1	<1
Wine, red, Shiraz	-	9.3	121.6	-	7.8	14.2
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.						

Table 3. Flavan-3-ol Content of Flavan-3-ol-rich Foods (mg/100 g or 100 mL*)

	Flavon-3-ol Monomers[#] and Thearubigins						
Food	**C**	**GC**	**EC**	**ECG**	**EGC**	**EGCG**	**Thearubigins**
Apples, Red Delicious, raw, with skin	2	0	9.8	0	<1	<1	-
Apricots, raw	3.7	0	4.7	0	0	0	-
Chocolate, dark	24.2	-	84.4	-	-	-	-
Tea, black, brewed	1.5	1.2	2.1	5.9	8	9.4	81.3
Tea, green, brewed	4.5	1.5	8.3	17.9	29.2	70.2	1.1
Tea, oolong, brewed	<1	-	2.5	6.3	6.1	34.5	-
Tea, white, brewed	-	-	-	8.3	18.6	42.4	-
Wine, red, Shiraz	6.8	-	10	-	-	-	-
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces. [#]Catechins: C, (+)-catechin; GC, (-)-gallocatechin; EC (-)-epicatechin; ECG, (-)-epigallocatechin; ECG, (-)-epicatechin gallate; EGCG, (-)-epigallocatechin gallate.							

Table 4. Proanthocyanidin Content of Flavan-3-ol-rich Foods (mg/100 g or 100 mL*)

	Proanthocyanidins (Flavon-3-ol Polymers)			
Food	**Monomers**	**Dimers**	**Trimers**	**≥4mers**
Apples, Red Delicious, raw, with skin	8.3	15.1	10.1	94.2
Baking chocolate, unsweetened	198.5	206.5	130.9	1,100
Cocoa, dry powder, unsweetened	316.6	183.5	159.5	713.4
Cranberries, raw	7.3	25.9	18.9	385.6
Currants, black, raw	<1	2.9	3	142.9
Grapes, red, raw	1.4	2.4	1	56.9
Nuts, pecan	17.2	42.1	26	408.6
Nuts, pistachio	10.9	13.3	10.5	202.6
Peaches, yellow, with peel, raw	4.5	12.2	4.4	50.6
Plums, with peel, raw	10.9	38.5	22.2	149.1
Spices, cinnamon, ground	23.9	256.3	1252.2	6,576
Strawberries, raw	3.7	5.3	4.9	127.8
Wine, table, red	16.6	20.5	1.8	22.7
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.				

Table 5. Flavonol Content of Flavonol-rich Foods (mg/100 g or 100 mL*)

	Flavonols			
Food	**Isorhamnetin**	**Kaempferol**	**Myricetin**	**Quercetin**
Blueberries, raw	-	1.7	1.3	7.7
Broccoli, raw	-	7.8	<1	3.3
Chili peppers, green, raw	-	0	1.2	14.7
Cowpea, black seeds, raw	-	1.9	2.7	17.2
Kale, raw	23.6	46.8	0	22.6
Onions, red, raw	4.6	<1	2.2	39.2
Parsley, fresh	0	1.5	14.8	<1
Rocket, wild, raw	<1	1.8	-	66.2
Scallions, raw	-	1.4	0	10.7
Spinach, raw	-	6.4	<1	4
Tea, black, brewed	-	1.4	<1	2.2
Tea, green, brewed	-	1.3	1	2.5
Watercress, raw	0	23	<1	30
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.				

Table 6. Flavone Content of Flavone-rich Foods (mg/100 g or 100 mL*)

	Flavones	
Food	**Apigenin**	**Luteolin**
Celery hearts, green	19.1	3.5
Celery, raw	2.8	1
Chili peppers, green, raw	1.4	3.9
Oregano, fresh	2.6	1
Parsley, fresh	215.5	1.1
Peppermint, fresh	5.4	12.7
Thyme, fresh	2.5	45.2
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.		

Table 7. Flavanone Content of Flavanone-rich Foods (mg/100 g or 100 mL*)

	Flavanones		
Food	**Eriodictyol**	**Hesperetin**	**Naringenin**
Grapefruit juice, white, fresh	<1	2.3	18.2
Grapefruit, white, raw	-	<1	21.3
Lemon juice, fresh	4.9	14.5	1.4
Lemon, raw	21.4	27.9	<1
Orange juice, fresh	<1	12	2.1
Orange, raw	-	27.2	15.3
Pummelo juice, fresh	2.9	1.8	25.3
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.			

Table 8. Isoflavone Content of Isoflavone-rich Foods (mg/100 g or 100 mL*)

	Isoflavones		
Food	**Diadzein**	**Genistein**	**Glycitein**
Black bean sauce	6	4	<1
Natto	33.2	37.7	10.5
Soybeans, mature seeds, raw	62.1	81	15
Soymilk, low-fat	1	1.5	<1
Tofu, firm, cooked	10.3	10.9	1.3
*per 100 g (fresh weight) or 100 mL (liquids); 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.			

Supplements

Anthocyanins

Bilberry, elderberry, black currant, blueberry, red grape, and mixed berry extracts that are rich in anthocyanins are available as dietary supplements without a prescription in the US. The anthocyanin content of these products may vary considerably. Standardized extracts that list the amount of anthocyanins per dose are available.

Flavan-3-ols

Numerous tea extracts are available in the US as dietary supplements and may be labeled as tea catechins or tea polyphenols. Green tea extracts are the most commonly marketed, but black and oolong tea extracts are also available. Green tea extracts generally have higher levels of catechins (flavan-3-ol monomers), while black tea extracts are richer in theaflavins and thearubigins (tea flavan-3-ol dimers and polymers, respectively). Oolong tea extracts fall somewhere in between green and black tea extracts with respect to their flavan-3-ol content. Some tea extracts contain caffeine, while others are decaffeinated. Flavan-3-ol and caffeine content vary considerably among different products, so it is important to check the label or consult the manufacturer to determine the amounts of flavan-3-ols and caffeine that would be consumed daily with each supplement (for more information on tea flavan-3-ols, see the article on Tea).

Flavanones

Citrus bioflavonoid supplements may contain glycosides of hesperetin (hesperidin), naringenin (naringin), and eriodictyol (eriocitrin). Hesperidin is also available in hesperidin-complex supplements, with daily doses from 500 mg to 2 g (153).

Flavones

The peels and tissues of citrus fruit (e.g., oranges, tangerines, and clementines) are rich in polymethoxylated flavones: tangeretin, nobiletin, and sinensetin (2). Although dietary intakes of these naturally occurring flavones are generally low, they are often present in citrus bioflavonoid complex supplements. Several dietary supplements may also contain various amounts of baicalein (aglycone) and/or baicalin (glycoside). Some tea preparations may also include baicalein-7-glucuronide (153).

Flavonols

The flavonol aglycone, quercetin, and its glycoside rutin are available as dietary supplements without a prescription in the US. Other names for rutin include rutoside, quercetin-3-rutinoside, and sophorin (153). Citrus bioflavonoid supplements may also contain quercetin or rutin.

Isoflavones

A 50-mg soy isoflavone supplement usually includes glycosides of the isoflavones: genistein (genistin; 25 mg), daidzein (daidzin; 19 mg), and glycitein (glycitin; about 6 mg). Smaller amounts of daidzein, genistein, and formononetin are also found in biochanin A-containing supplements (derived from red clover) (153).

Safety

Adverse effects

No adverse effects have been associated with high dietary intakes of flavonoids from plant-based food. This lack of adverse effects may be explained by the relatively low bioavailability and rapid metabolism and elimination of most flavonoids.

Quercetin

Oral supplementation with quercetin glycosides at doses ranging between 3 mg/day-1,000 mg/day for up to three months has not resulted in significant adverse effects in clinical studies (reviewed in 154). A randomized, placebo-controlled study in 30 patients with chronic prostatitis reported one case of headache and another of tingling of the extremities associated with supplemental quercetin (1,000 mg/day for one month); both issues resolved after the study ended (155). In a phase I clinical trial in cancer patients unresponsive to standard treatments, administration of quercetin via intravenous infusion resulted in symptoms of nausea, vomiting, sweating, flushing, and dyspnea (difficulty breathing) at doses ≥10.5 mg/kg body weight (~756 mg of quercetin for a 70 kg individual) (156). Higher doses up to 51.3 mg/kg body weight (~3,591 mg of quercetin) were associated with renal (kidney) toxicity, yet without evidence of nephritis, infection, or obstructive uropathy (reviewed in 154).

Cocoa flavan-3-ols

In a recent randomized, double-blind, controlled study in healthy adults, the daily intake of 2 g of cocoa flavan-3-ols for 12 weeks was found to be well tolerated with no adverse side effects (157).

Tea extracts

In clinical trials employing caffeinated green tea extracts, cancer patients who took 6 g/day in three to six divided doses reported mild-to-moderate gastrointestinal side effects, including nausea, vomiting, abdominal pain, and diarrhea (158, 159). Central nervous system symptoms, including agitation, restlessness, insomnia, tremors, dizziness, and confusion, have also been reported. In one case, confusion was severe enough to require hospitalization (158). In a systematic review published in 2008, the US Pharmacopeia (USP) Dietary Supplement Information Expert Committee identified 34 adverse event reports implicating the use of green tea extract products (containing 25%-97% of polyphenols) as the likely cause of liver damage (hepatotoxicity) in humans (160). In a four-week clinical trial that assessed the safety of decaffeinated green tea extracts (800 mg/day of EGCG) in healthy individuals, a few of the participants reported mild nausea, stomach upset, dizziness, or muscle pain (161). In the Minnesota Green Tea Trial (MGTT), 1,075 postmenopausal women were randomized to receive green tea extracts (1,315±116 mg/day of catechins; the equivalent of four 8-ounce mugs of brewed decaffeinated green tea) or a placebo for one year. The total number of adverse events and the number of serious adverse events were not different between the treatment and placebo groups (162). However, the use of green tea extracts was directly associated with abnormally high liver enzyme levels in 7 out of the 12 women who experienced serious adverse events. Also, the incidence of nausea was twice as high in the green tea arm as in the placebo group (162).

Pregnancy and lactation

The safety of flavonoid supplements in pregnancy and lactation has not been established (153).

Drug interactions

Inhibition of ABC drug transporters

ATP-binding cassette (ABC) drug transporters, including P-glycoprotein, multidrug resistance protein (MRP), and breast cancer-resistant protein (BCRP), function as ATP-dependent efflux pumps that actively regulate the excretion of a number of drugs limiting their systemic bioavailability (8). ABC transporters are found throughout the body, yet they are especially important in organs with a barrier function like the intestines, the blood-brain barrier, blood-testis barrier, and the placenta, as well as in liver and kidneys (163). There is some evidence that the consumption of grapefruit juice inhibits the activity of P-glycoprotein (164). Genistein, biochanin A, quercetin, naringenin, hesperetin, green tea flavan-3-ol (-)-CG, (-)-ECG, and (-)-EGCG, and others have been found to inhibit the efflux activity of P-glycoprotein in cultured cells and in animal models (163). Thus, very high or supplemental intakes of these flavonoids could potentially increase the toxicity of drugs that are substrates of P-glycoprotein, e.g., digoxin, antihypertensive agents, antiarrhythmic agents, chemotherapeutic (anticancer) agents, antifungal agents, HIV protease inhibitors, immunosuppressive agents, H_2 receptor antagonists, some antibiotics, and others (reviewed in 165).

Many anthocyanins and anthocyanidins, as well as some flavones (apigenin, chrysin), isoflavones (biochanin A, genistein), flavonols (kaempferol), and flavanones (naringenin), have been identified as inhibitors of BRCP-mediated transport, theoretically affecting drugs like anticancer agents (mitoxantrone, topotecan, thyrosine kinase inhibitors), antibiotics (fluoroquinolones), β-blockers (prazosin), and antiarthritics (sulfasalazine). Finally, flavonols (quercetin, kaempferol, myricetin), flavanones (naringenin), flavones (apigenin, robinetin), and isoflavones (genistein) have been reported to inhibit MRP, potentially affecting MRP-mediated transport of many anticancer drugs, e.g., vincristin, etoposide, cisplatin, irinotecan, methotrexate, camptothecin, anthracyclines, vinca alkaloids (reviewed in 163).

Anticoagulant and antiplatelet drugs

High intakes of flavonoids from purple grape juice (500 mL/day) and dark chocolate (235 mg/day of flavan-3-ols) have been found to inhibit platelet aggregation in *ex vivo* assays (166-169). Theoretically, high intakes of flavonoids (e.g., from supplements) could increase the risk of bleeding when taken with anticoagulant drugs, such as warfarin (Coumadin), heparin, dalteparin (Fragmin), enoxaparin (Lovenox), and antiplatelet drugs, such as clopidogrel (Plavix), dipyridamole (Persantine), non-steroidal anti-inflammatory drugs (NSAIDs: diclofenac, ibuprofen, naproxen), aspirin, and others (170).

Inhibition of CYP 3A4 by flavonoid-rich grapefruit

Cytochrome P450 (CYP) enzymes are phase I biotransformation enzymes involved in the metabolism of a broad range of compounds, from endogenous molecules to therapeutic agents. The most abundant CYP isoform in the liver and intestines is cytochrome P450 3A4 (CYP3A4); the CYP3A family catalyzes the metabolism of about one-half of all marketed drugs in the US and Canada (171). One grapefruit or as little as 200 mL (7 fluid ounces) of grapefruit juice have been found to irreversibly inhibit intestinal CYP3A4 (164). The most potent inhibitors of CYP3A4 in grapefruit are thought to be furanocoumarins, particularly dihydroxybergamottin, rather than flavonoids. All forms of the fruit — freshly squeezed juice, frozen concentrate, or whole fruit — can potentially affect the activity of CYP3A4. Some varieties of other citrus fruit (Seville oranges, limes, and pomelos) that contain furanocoumarins can also interfere with CYP3A4 activity.

Specifically, the inhibition of intestinal CYP3A4 by grapefruit consumption is known or predicted to increase the bioavailability and the risk of toxicity of more than 85 drugs. Because drugs with very low bioavailability are more likely to be toxic when CYP3A4 activity is inhibited, they are associated with a higher risk of overdose with grapefruit compared to drugs with high bioavailability. Some of the drugs with low bioavailability include, but are not limited to, anticancer drugs (everolimus); anti-infective agents halofantrine, maraviroc); statins (atorvastatin, lovastatin, and simvastatin); cardioactive drugs (amiodarone, clopidogrel, dronedarone, eplenorone, ticagrelor); HIV protease inhibitors (saquinavir), immunosuppressants (cyclosporine, sirolimus, tacrolimus, everolimus); antihistamines (terfenadine); gastrointestinal agents (domperidone); central nervous system agents (buspirone, dextromethorphan, oral ketamine, lurasidone, quetiapine, selective serotonin reuptake inhibitors [sertraline]); and urinary tract agents (darifenacin) (reviewed in 171). Because of the potential for adverse drug interactions, some clinicians recommend that people taking medications with low bioavailability (i.e., undergoing extensive metabolism by CYP3A4) avoid consuming grapefruit and grapefruit juice altogether during the treatment period (171).

Nutrient interactions

Iron

Flavonoids can bind nonheme iron, inhibiting its intestinal absorption (172, 173). Nonheme iron is the principal form of iron in plant foods, dairy products, and iron supplements. The consumption of one cup of tea or cocoa with a meal has been found to decrease the absorption of nonheme iron in that meal by about 70% (174, 175). Flavonoids can also inhibit intestinal heme iron absorption (176). Interestingly, ascorbic acid greatly enhances the absorption of iron (see the article on Iron) and is able to counteract the inhibitory effect of flavonoids on nonheme and heme iron absorption (173, 176, 177). To maximize iron absorption from a meal or iron supplements, flavonoid-rich food and beverages and flavonoid supplements should not be consumed at the same time.

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Garlic

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Indole-3-Carbinol

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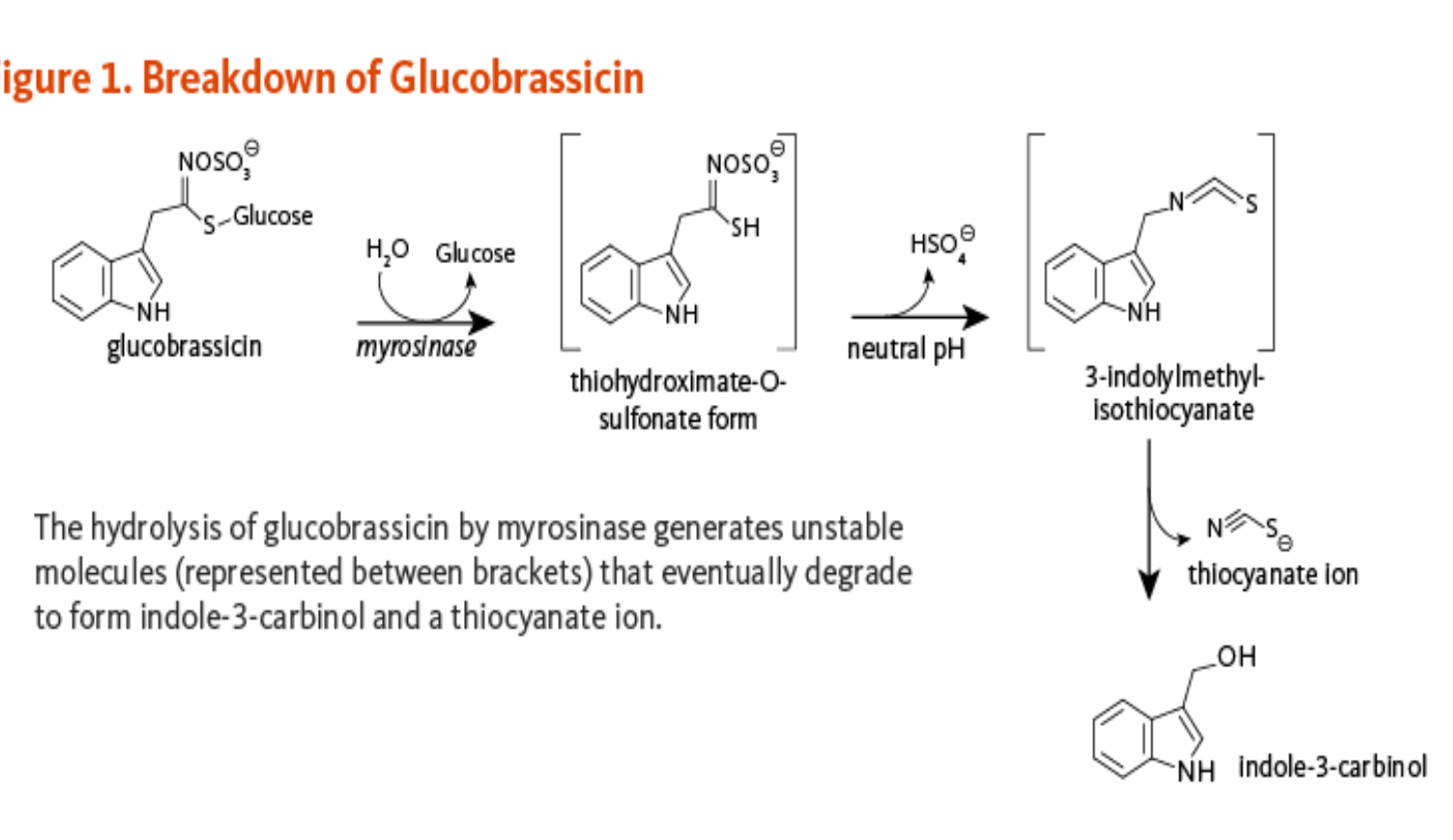
Summary

- Indole-3-carbinol (I3C) is derived from the breakdown of glucobrassicin, a compound found in cruciferous vegetables. *(More information)*
- In the stomach, I3C molecules undergo acid-catalyzed condensation that generates a number of biologically active I3C oligomers, such as 3,3'-diindolylmethane (DIM) and 5,11-dihydroindolo-[3,2-*b*]carbazole (ICZ). *(More information)*
- I3C and DIM have been found to modulate the expression and activity of biotransformation enzymes that are involved in the metabolism and elimination of many biologically active compounds, including steroid hormones, drugs, carcinogens, and toxins. *(More information)*
- Preclinical studies suggested that anti-estrogenic activities of I3C and DIM might help reduce the risk of hormone-dependent cancers. Although supplementation with I3C and DIM could alter urinary estrogen metabolite profiles in women, the effects of I3C and DIM on breast cancer risk are not known. *(More information)*
- Preclinical studies showed that I3C and I3C oligomers could affect multiple signaling pathways that are dysregulated in cancer cells, such as those controlling cell proliferation, apoptosis, migration, invasion, and angiogenesis. *(More information)*
- Limited evidence from preliminary trials suggested that I3C supplementation may help treat conditions related to human papilloma virus (HPV) infection, such as cervical/vulvar intraepithelial neoplasias and recurrent respiratory papillomatosis. However, randomized controlled trials are needed to determine whether I3C supplementation is beneficial. *(More information)*
- The timing of I3C exposure in animal models of chemically-induced cancers seems to determine whether I3C inhibits or promotes the development of tumors. Some experts have cautioned against the widespread use of I3C and DIM supplements for cancer prevention in humans until their potential risks and benefits are better understood. *(More information)*

Introduction

Some observational studies have reported significant associations between high intakes of cruciferous vegetables and lower risk of several types of cancer (1). Cruciferous vegetables differ from other classes of vegetables in that they are rich sources of sulfur-containing compounds known as glucosinolates (for detailed information, see the article on Cruciferous Vegetables) (2). The potential health benefits of consuming cruciferous vegetables are attributed to compounds derived from the enzymatic hydrolysis (breakdown) of glucosinolates. Among these compounds is indole-3-carbinol (I3C), a compound derived from the degradation of an indole glucosinolate commonly known as glucobrassicin (**Figure 1**).

Figure 1. Breakdown of Glucobrassicin



The hydrolysis of glucobrassicin by myrosinase generates unstable molecules (represented between brackets) that eventually degrade to form indole-3-carbinol and a thiocyanate ion.

[Figure 1 - Click to Enlarge]

Metabolism and Bioavailability

A number of commonly consumed cruciferous vegetables, including broccoli, Brussels sprouts, and cabbage, are good sources of glucobrassicin — the glucosinolate precursor of I3C (see Food sources).

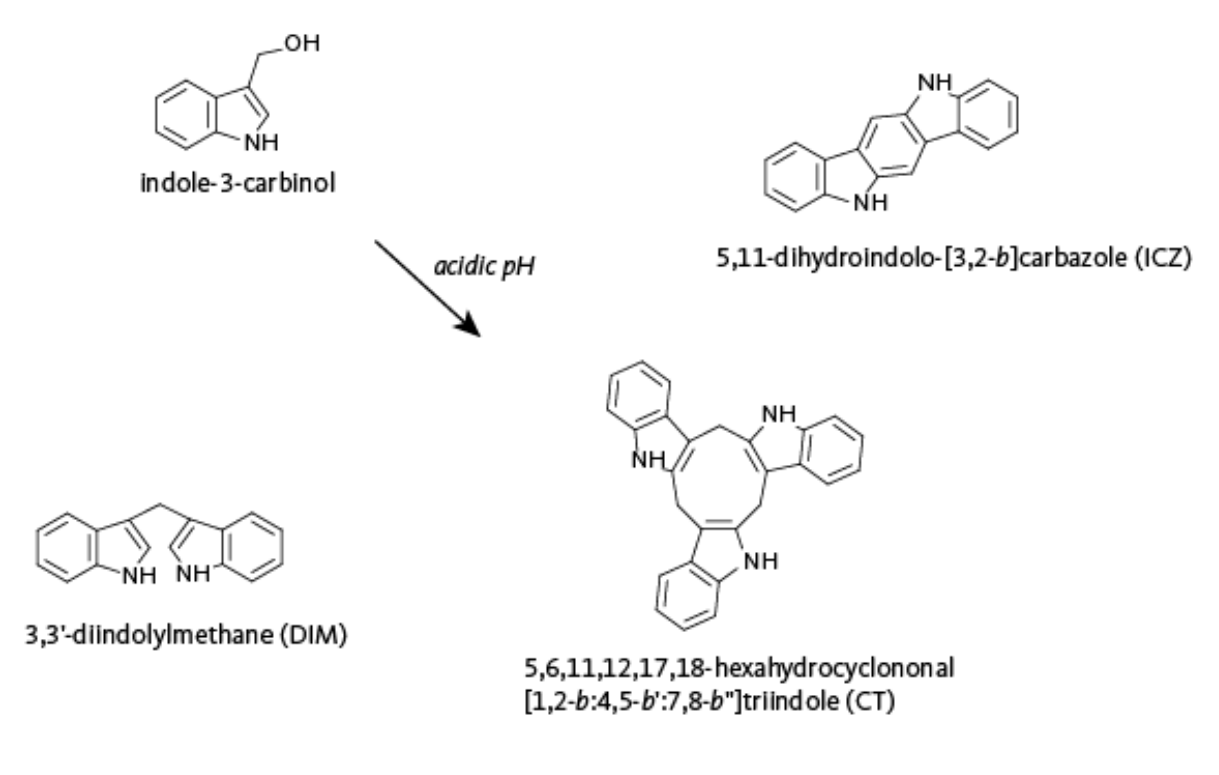
Myrosinase (β-thioglucosidase), an enzyme that catalyzes the hydrolysis of glucosinolates, is physically separated from glucosinolates in intact plant cells (3). When raw cruciferous vegetables are chopped or chewed, plant cells are damaged such that glucobrassicin is exposed to myrosinase. The hydrolysis of glucobrassicin initially produces a glucose molecule and the unstable aglycone, thiohydroximate-O-sulfonate. The spontaneous release of a sulfate ion results in the formation of another unstable intermediate form, 3-indolylmethylisothiocyanate (4). This compound easily splits into thiocyanate ion and I3C (**Figure 1**). In the acidic environment of the stomach, I3C molecules can combine with each other to form a complex mixture of polycyclic aromatic compounds, known collectively as acid condensation products (**Figure 2**) (5). Some of the most prominent acid condensation products include 3,3'-diindolylmethane (DIM), 5,11-dihydroindolo-[3,2-*b*]carbazole (ICZ), and a cyclic triindole (CT) (**Figure 2**). The biological activities of individual acid condensation products may differ from those of I3C (see Biological Activities).

When cruciferous vegetables are cooked, plant myrosinase is inactivated thus the hydrolysis of glucosinolates is prevented. Intact glucosinolates then transit to the colon and are metabolized by human intestinal bacteria. The generation of I3C from glucobrassicin may still occur to a lesser degree in the large intestine, due to the myrosinase activity of colonic bacteria (4). Thus, when cruciferous vegetables are cooked, I3C can still form in the colon, but I3C-derived acid condensation products are less likely to form in the more alkaline environment of the intestine.

No I3C could be detected in plasma following oral administration of single doses of I3C, ranging from 200 to 1,200 mg, to healthy women at high risk for breast cancer (6). However, DIM was detected and peaked in plasma around two hours after I3C ingestion, at concentrations from <100 nanograms per milliliter (ng/mL) with oral doses of 400 to 600 mg of I3C up to 500 ng/mL-600 ng/mL with oral doses of 1,000 to 1,200 mg of I3C. All DIM disappeared from the blood within 24 hours (6).

Formulation strategies, such as the encapsulation of I3C and DIM into nanoparticles or liposomes (7-9), are being developed with the aim of increasing the bioavailability and evaluating the safety and efficacy of these compounds in humans.

Figure 2. Condensation Derivatives of Indole-3-Carbinol



indole-3-carbinol
acidic pH
5,11-dihydroindolo-[3,2-b]carbazole (ICZ)
3,3'-diindolylmethane (DIM)
5,6,11,12,17,18-hexahydrocyclonona[1,2-b:4,5-b':7,8-b'']triindole (CT)

[Figure 2 - Click to Enlarge]

Biological Activities

Effects on biotransformation enzymes

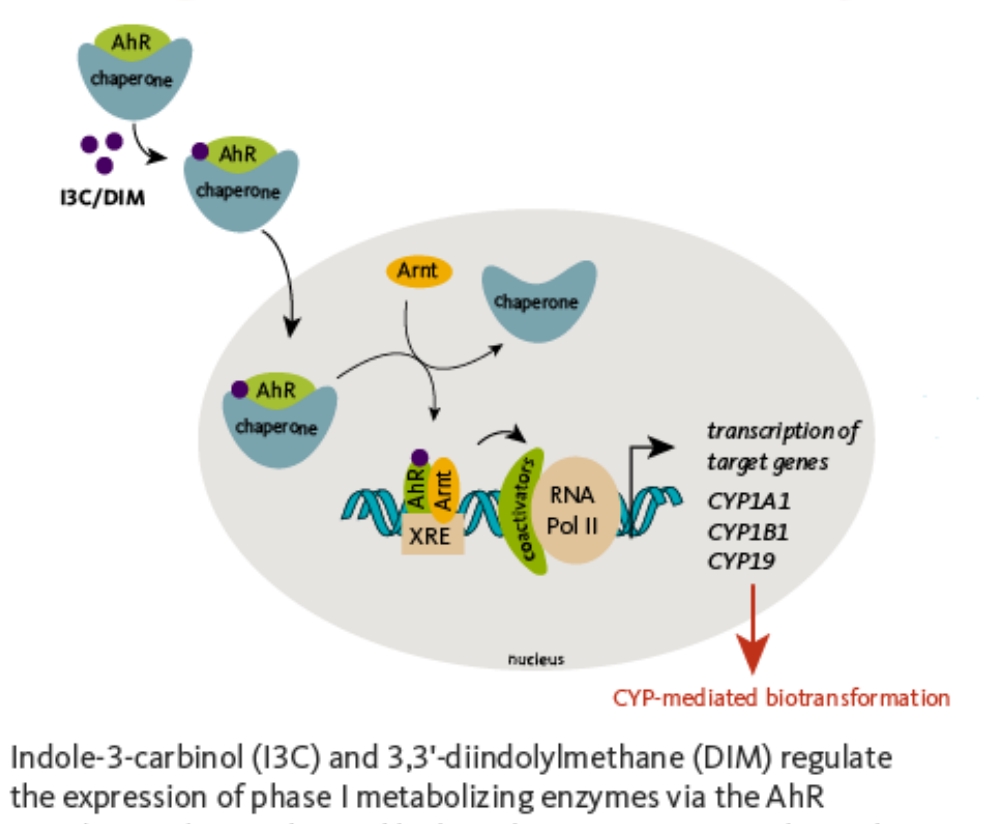
Biotransformation enzymes play major roles in the metabolism and elimination of many biologically active compounds, including physiologic regulators (e.g., estrogens), drugs, and environmental chemicals (xenobiotics; e.g., carcinogens, toxins). In general, phase I metabolizing enzymes, including the cytochrome P450 (CYP) family, catalyze reactions that increase the reactivity of hydrophobic (fat-soluble) compounds, which prepares them for reactions catalyzed by phase II detoxifying enzymes. Reactions catalyzed by phase II enzymes usually increase water solubility and promote the elimination of these compounds (10).

Aryl hydrocarbon receptor (AhR) pathway

I3C and some I3C condensation products can bind to a protein in the cytoplasm of cells called the aryl hydrocarbon receptor (AhR) (**Figure 3**) (11-13). In fact, ICZ is one of the most potent ligands for the AhR known with an affinity approaching that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). I3C acid condensation products, as well as indoles and their acid condensation products formed from tryptophan metabolism, appear to be important endogenous ligands for the AhR (13). Binding allows AhR to enter the nucleus where it forms a complex with the AhR nuclear translocator (Arnt) protein. This AhR/Arnt complex binds to specific DNA sequences, known as xenobiotic response elements (XRE), in the regulatory regions (promoters) of target genes, especially those involved in xenobiotic metabolism (14). The promoters of genes coding for a number of CYP enzymes and several phase II enzymes contain XREs. Microarray gene expression profiling of I3C- or DIM-treated human prostate cancer cells showed that both compounds upregulated the phase I enzyme, CYP1A1, and the phase II enzymes, glutathione S-transferase theta-1 (GST q1) and aldo-keto reductase (15). Another study in human prostate cancer cells demonstrated that the removal of AhR abolished I3C- or DIM-induced CYP1A1 mRNA expression (16). The expression of CYP1A1 and CYP1A2 was also upregulated in human primary liver cells challenged with DIM (17). Further, I3C and DIM have been found to interfere with CYP activities involved in estrogen metabolism (see Anti-estrogenic activities).

Increasing the activity of biotransformation enzymes is generally considered a beneficial effect because the elimination of potential carcinogens or toxins is enhanced. However, there is a potential for adverse effects because some procarcinogens require biotransformation by phase I enzymes to become active carcinogens (18).

Figure 3. I3C and DIM Regulate Phase I Biotransformation Enzymes via AhR Signaling



Indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM) regulate the expression of phase I metabolizing enzymes via the AhR signaling pathway. *AhR, aryl hydrocarbon receptor; Arnt, AhR nuclear translocator; CYP, cytochrome P450; RNA Pol II, RNA polymerase II; XRE, xenobiotic response element.*

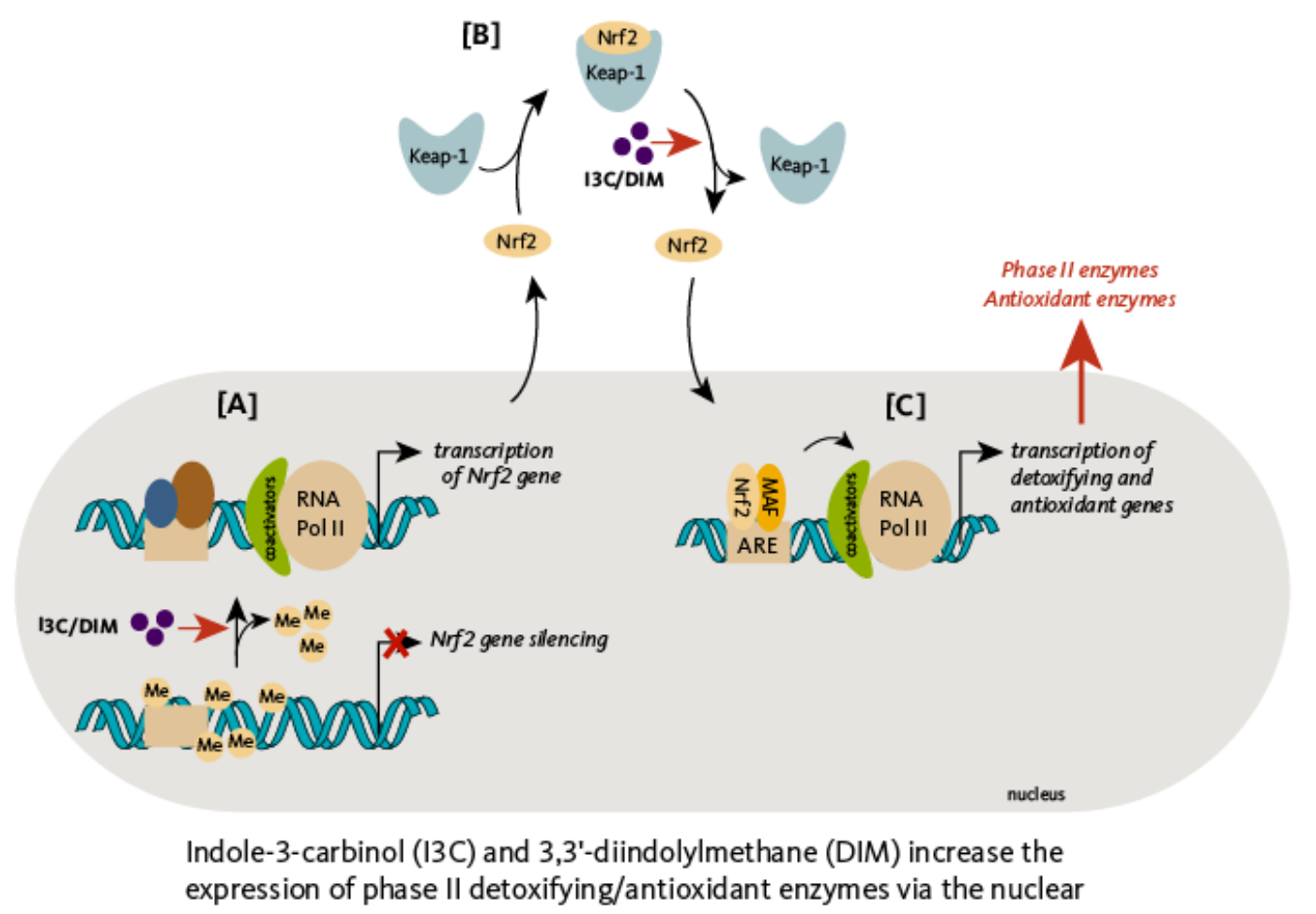
[Figure 3 - Click to Enlarge]

Nuclear factor E2-related factor 2-dependent pathway

I3C and DIM have been shown to induce the expression of phase II detoxifying and antioxidant enzymes via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway.

Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol (**Figure 4**). Keap1 responds to oxidative stress signals or chemical inducers by freeing Nrf2. Upon release, Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE) located in the promoters of genes coding for antioxidant/detoxifying enzymes and scavengers. Nrf2/ARE-dependent genes code for numerous mediators of the antioxidant response, including glutathione S-transferases (GSTs), thioredoxin, NAD(P)H quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) (19). DIM induced Nrf2/ARE-dependent upregulation of HO-1, and I3C stimulated NQO-1 and GST (μ2 isoform) expression in liver cancer cells (20). In addition, the transcription of *Nrf2* coding gene, which was abnormally repressed through promoter DNA hypermethylation, was enhanced in mouse prostate cancer cells treated with DIM. DIM subsequently restored the expression of the Nrf2-target genes, *NQO1* and *GSTμ1* (21). DIM also reversed *Nrf2* gene silencing in transgenic mouse prostate cancer tissues, including Nrf2 expression, and subsequently, NQO1 expression (**Figure 4**). This was accompanied by the suppression of proliferation and the induction of apoptosis in prostate cancer tissues (21). Similar observations have been reported with I3C (22).

Figure 4. I3C and DIM Regulate Phase II Biotransformation Enzymes via Nrf2 Signaling



Indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM) increase the expression of phase II detoxifying/antioxidant enzymes via the nuclear factor E2-related factor 2 (Nrf2) signaling pathway. [A] I3C and DIM restore the transcription of Nrf2 gene by reversing promoter methylation, [B] I3C and DIM induce the nuclear translocation of Nrf2, and [C] I3C and DIM increase the expression of Nrf2 target genes coding for phase II enzymes and antioxidant enzymes. *ARE, antioxidant response element; Keap-1, Kelch-like ECH-associated protein 1; MAF, Nrf2 transcriptional cofactor; Me, methyl group; RNA Pol II, RNA polymerase II.*

[Figure 4 - Click to Enlarge]

Anti-estrogenic activities

Endogenous estrogens are steroid hormones synthesized by humans and other mammals.

Inhibition of estrogen synthesis

In breast tissue, CYP19 (aromatase) catalyzes the final steps in the conversion of androgens (testosterone or androstenedione) to estrogens (17β-estradiol or estrone, respectively). Both I3C and DIM have been found to downregulate the expression of CYP19 in non-tumorigenic and tumorigenic estrogen-responsive (ER$^+$) breast cells, whereas CYP19 expression was increased in I3C/DIM-treated tumorigenic estrogen-independent (ER$^-$) breast cells (23).

Inhibition of estrogen metabolic activation

Prolonged exposure to estrogens is thought to play a role in cancer development through CYP-mediated generation of estrogen reactive metabolites that can damage DNA (24, 25).

Phase I metabolizing enzymes, CYP1A1, CYP1A2, and CYP1B1, have been involved in the oxidative metabolism of estrogens. 17β-estradiol can be converted to 2-hydroxyestradiol (2HE$_2$) and 4-hydroxyestradiol (4HE$_2$) by CYP1A1/2 and CYP1B1, respectively. 2HE$_2$ and 4HE$_2$ are further metabolized to 2- and 4-metoxymetabolites by the phase II enzyme, catechol-*O*-methyltransferase (COMT) (25). 2HE$_2$ is a noncarcinogenic agent with weaker estrogenic potential than 17β-estradiol, while 4-HE$_2$ can be converted to free radicals that can form DNA adducts and promote carcinogenesis (26, 27). In different breast cancer cell lines, I3C and DIM have been shown to upregulate the expression of CYP1A1, CYP1A2, and CYP1B1 at the transcript (mRNA) level but not at the protein level (28).

Additionally, the endogenous estrogens 17β-estradiol and estrone can be irreversibly metabolized to 16a-hydroxyestrone (16HE$_1$) (29). In contrast to 2-hydroxyestrone (2HE$_1$), 16HE$_1$ is highly estrogenic and has been found to stimulate the proliferation of several estrogen-sensitive cancer cell lines (30, 31). It has been hypothesized that shifting the metabolism of 17β-estradiol toward 2HE$_1$, and away from 16HE$_1$, could decrease the risk of estrogen-sensitive cancers, such as breast cancer (32). In controlled clinical trials, oral supplementation with I3C or DIM has consistently increased urinary 2HE$_1$ concentrations or urinary 2HE$_1$:16HE$_1$ ratios in women (33-39). However, large case-control and prospective cohort studies have failed to find significant associations between urinary 2HE$_1$:16HE$_1$ ratios and risk of breast and endometrial cancer (40-43).

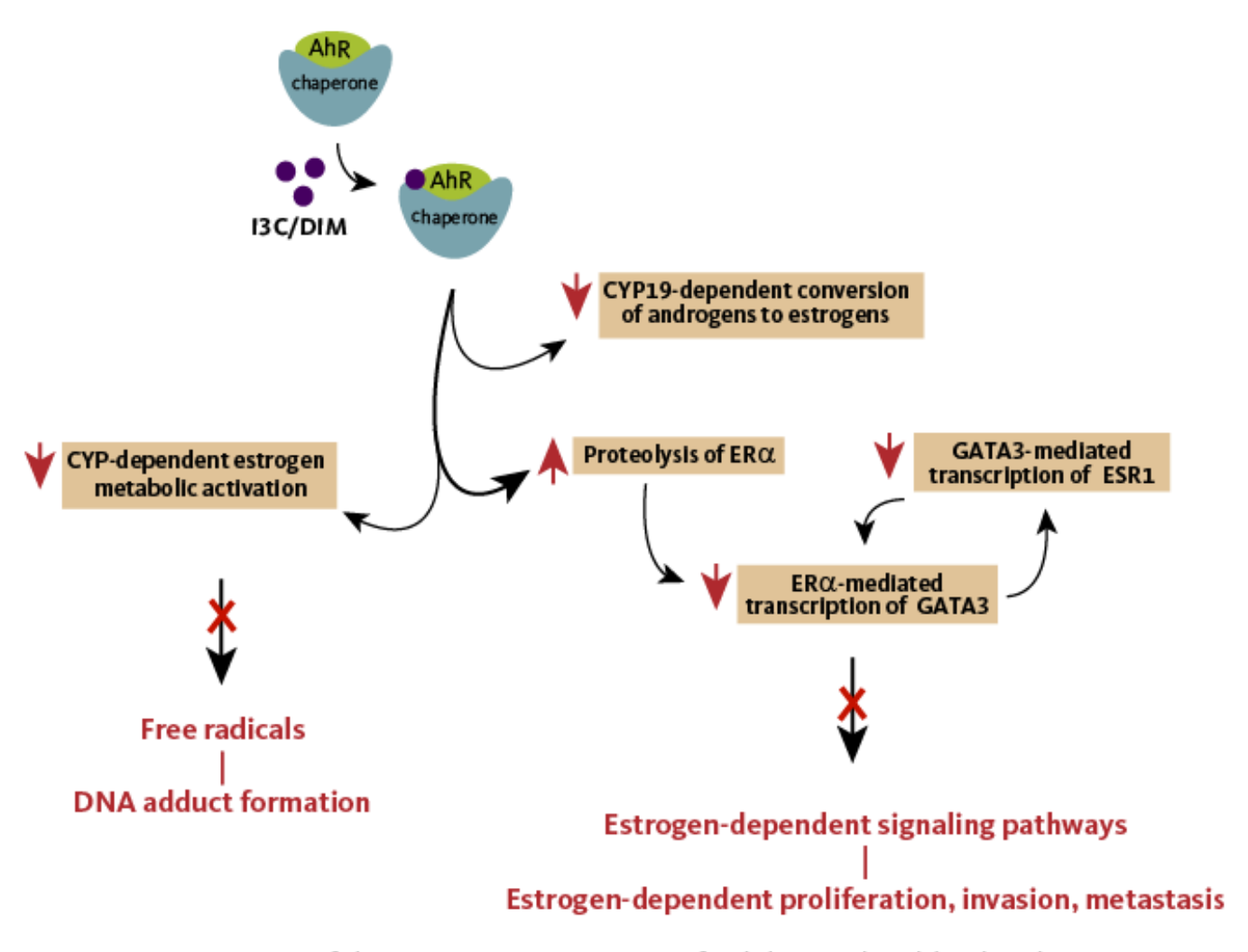
Inhibition of estrogen signaling

Endogenous estrogens, including 17β-estradiol, exert their estrogenic effects by binding to specific nuclear receptors called estrogen receptors (ERs). Within the nucleus, estrogen-activated ERs can bind to specific DNA sequences, known as estrogen response elements (EREs), in the promoters of estrogen-responsive genes. ERE-bound estrogen-ER complexes act as transcription factors by recruiting coactivator proteins and chromatin remodeling factors to promoters, thereby triggering the transcription of target genes (44). There are two major ER subtypes, ERα and ERβ, coded by two separate genes *ESR1* and *ESR2*, respectively. ERα is the main driver of the proliferative effect of estrogens, while the expression of ERβ has been inversely associated with mammary gland tumorigenesis (45). Elevated ERα levels promote cellular proliferation in the breast and uterus, possibly increasing the risk of developing estrogen-sensitive cancers (46).

Inhibition of estrogen-dependent cell proliferation

In estrogen-sensitive human breast cancer cells challenged with 17β-estradiol, I3C has been found to inhibit the transcription of estrogen-responsive genes without binding to either ERβ or ERα (47, 48). In fact, the binding of I3C to AhR was shown to trigger the proteasome-dependent degradation of ERα (49). I3C-induced loss of ERα resulted in the downregulation of ERα-responsive gene products like the transcription factor GATA3. Since GATA3 regulates the transcription of the ERα coding gene *ESR1*, I3C prevented the synthesis of new ERα transcripts and proteins, eventually abolishing the ERα signaling pathway. The disruption of the GATA3/ERα cross-regulatory loop by I3C ultimately halted ERα-dependent cell proliferation (49). Acid condensation products of I3C that bind and activate AhR may also inhibit the transcription of estrogen-responsive genes by competing for co-activators or increasing ERα degradation (14, 50). I3C treatment also affected the expression of other ERα-responsive genes, including those coding for insulin-like growth factor-1 receptor (IGFR1) and insulin receptor substrate-1 (IRS-1), involved in cell proliferation and deregulated in breast cancer (**Figure 5**) (51).

Figure 5. Overview of Anti-estrogenic Actions of I3C and DIM



AhR
chaperone
I3C/DIM
AhR
chaperone
CYP19-dependent conversion of androgens to estrogens
CYP-dependent estrogen metabolic activation
Proteolysis of ERα
GATA3-mediated transcription of ESR1
ERα-mediated transcription of GATA3
Free radicals
DNA adduct formation
Estrogen-dependent signaling pathways
Estrogen-dependent proliferation, invasion, metastasis

Overview of the anti-estrogenic actions of indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM). *AhR, aryl hydrocarbon receptor; CYP, cytochrome P450; ERα, estrogen receptor α; ESR1, gene encoding ERα.*

[Figure 5 - Click to Enlarge]

Modulation of cell-signaling pathways

I3C and condensation derivatives have been found to affect multiple signaling pathways that are often deregulated in cancer cells. Below are some examples illustrating how I3C, DIM, or ICZ may influence cell proliferation, apoptosis, migration, invasion, angiogenesis, and immunity by targeting specific signaling pathways (23).

Induction of cell cycle arrest and apoptosis

Once a cell divides, it passes through a sequence of stages — collectively known as the cell cycle — before it divides again. Following DNA damage, the cell cycle can be transiently arrested at damage checkpoints, which allows for DNA repair or activation of pathways leading to cell death (apoptosis) if the damage is irreparable (52). Defective cell cycle regulation may result in the propagation of mutations that contribute to the development of cancer. In addition, unlike normal cells, cancerous cells lose their ability to respond to death signals that initiate apoptosis.

I3C-induced downregulation of the phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (Akt) cell survival signaling pathway in mice with nasopharyngeal carcinoma resulted in inhibition of cell proliferation and induction of apoptosis (53). Inactivation of the Wnt/β-catenin signaling pathway in DIM-treated colon cancer cells decreased the expression of downstream targets, c-myc and cyclin D1, that promote cell proliferation and survival (54). In prostate cancer cells, I3C opposed the anti-apoptotic effect of epidermal growth factor (EGF) by limiting EGF receptor autophosphorylation (activation) and reducing EGF-induced activation of the PI3K/Akt signaling pathway and expression of the pro-survival target molecules, Bcl-x(L) and BAD (55). In another study, DIM caused apoptosis of prostate cancer cells by stimulating p38 mitogen-activated protein kinase (p38 MAPK)-induced upregulation of tumor suppressor p75^{NTR} (56). The anti-proliferative effect of DIM in cancer cells has also been linked to the inhibition of histone deacetylase (HDAC) activity. Specifically, DIM was found to reverse HDAC-mediated epigenetic silencing of genes coding for key regulators of the cell cycle (57, 58). A recent genome-wide analysis of DNA methylation also showed that DIM could reverse aberrant promoter methylation in prostate cancer cells, at least partly through downregulating the expression of DNA methyltransferases (DNMTs) (59).

Inhibition of cell migration and invasion

The epithelial-to-mesenchymal transition (EMT) describes a process of epithelial cell transformation whereby cells lose their polarity and adhesion properties while gaining migratory and invasive properties through the expression of mesenchymal genes. Inhibition of EMT by I3C and ICZ in breast cancer cells has been associated with upregulation of an epithelial marker, E-cadherin, and downregulation of vimentin, focal adhesion kinase (FAK), and matrix metalloproteins (MMPs) — proteins and enzymes known to promote migration (60). DIM also inhibited migration and invasion of liver cancer cells *in vitro* and *in vivo* through inactivating the FAK signaling pathway (61). Moreover, DIM has been shown to reverse methylation-associated dysregulation of genes involved in cell adhesion, chemotaxis, and inflammation that contributes to cancer progression (59). DIM was able to inhibit lung metastasis in mice with liver (61) or mammary tumors (62).

Inhibition of angiogenesis

To fuel their rapid growth, invasive tumors must also develop new capillaries from preexisting blood vessels by a process known as angiogenesis. I3C inhibited lipopolysaccharide (LPS)-induced macrophage activation and secretion of proangiogenic molecules, such as nitric oxide (NO), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and MMP-9, and prevented the formation of capillary-like structures from co-cultured human umbilical endothelial cells (63). Similarly, I3C inhibited capillary-like tube formation from phorbol myristate acetate (PMA)-stimulated endothelial cells (64). DIM also blocked PMA-induced angiogenic activities in human umbilical endothelial cells (65).

Regulation of inflammation and cell-mediated immunity

Uncontrolled inflammation has been associated with several chronic diseases, including cancer. In the mouse ear edema model, 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced upregulation of pro-inflammatory mediators, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), has been found to be mitigated by DIM treatment (66). Nuclear factor-kappa B (NF-κB) is a major transcription factor regulating the expression of many pro-inflammatory genes like those coding for COX-2 and iNOS. Specifically, DIM inhibited TPA-induced activation of kinases (inhibitor of kappa B kinase [IκK] and extracellular signal-regulated kinase [ERK]) that control the transcriptional activity of NF-κB (66). In addition, recent animal studies showed that I3C and/or DIM could modulate cell-mediated immune response in experimental autoimmune encephalomyelitis (67), staphylococcal enterotoxin-induced lung inflammation (68), and delayed-type hypersensitivity (69). Specifically, I3C and/or DIM differentially regulated T-cell subpopulations via the activation or suppression of microRNA-dependent pathways controlling cell cycle progression and apoptosis.

Transplacental cancer prevention

The inclusion of I3C in the maternal diet was found to protect the offspring from lymphoma and lung tumors induced by dibenzo[*a*]pyrene, a polycyclic aromatic hydrocarbon (70, 71). Polycyclic aromatic hydrocarbons are chemical pollutants formed during incomplete combustion of organic substances, such as coal, oil, wood, and tobacco (72).

However, the physiological relevance of cell culture and animal studies to human health is unclear since little or no I3C is available to tissues after oral administration (see Metabolism and Bioavailability) (6).

Disease Prevention

Cancer

Some observational studies provide some support for the hypothesis that higher intakes of cruciferous vegetables are associated with lower risk for some types of cancer (see the article on Cruciferous Vegetables) (1). Cruciferous vegetables are relatively good sources of nutrients that may have protective effects against cancer, including vitamin C, folate, selenium, carotenoids, and fiber. In addition, glucosinolates can be hydrolyzed to a variety of potentially protective isothiocyanates, in addition to indole-3-carbinol (see the article on Isothiocyanates). Consequently, evidence for an inverse association between cruciferous vegetable intake and cancer risk provides relatively little information about the specific effects of indole-3-carbinol on cancer risk.

At present, the effects of I3C or DIM supplementation on cancer risk in humans are not known.

Disease Treatment

Human papilloma virus infection-related diseases

Cervical intraepithelial neoplasia

Infection with certain strains of human papilloma virus (HPV) is an important risk factor for cervical cancer (73). Transgenic mice that express cancer-promoting HPV genes develop cervical cancer with chronic 17β-estradiol administration. In this model, feeding I3C markedly reduced the number of mice that developed cervical cancer (74). A small placebo-controlled trial in women examined the effect of oral I3C supplementation on the progression of precancerous cervical lesions classified as cervical intraepithelial neoplasia (CIN) 2 or CIN 3 (75). After 12 weeks, four out of the eight women who took 200 mg/day had complete regression of CIN, and four out of the nine who took 400 mg/day had complete regression; none of the 10 women who took a placebo had complete regression. HPV was present in 7 out of the 10 women in the placebo group, seven out of eight women in the 200 mg I3C group, and eight out of nine women in the 400 mg I3C group (75). However compared to placebo, oral supplementation with DIM (2 mg/kg/day) for 12 weeks in 64 women with CIN 2 or CIN 3 lesions failed to improve clinical parameters during a one-year follow-up period (76). In another six-month randomized, double-blind controlled trial, DIM supplementation (150 mg/day) failed to promote HPV clearance and prevent CIN progression in 551 women with low-grade cell abnormalities in cervical smears (77).

Although oral supplementation of I3C or DIM appears relatively safe and well tolerated, results obtained with I3C are only preliminary, and interventions with DIM failed to show preventative or therapeutic efficacy in women with precancerous lesions of the cervix. The intravaginal administration of DIM in the form of suppositories may prove to be a more effective approach to reverse CIN in women (78).

Vulvar intraepithelial neoplasia

HPV infection has also been associated with vulvar intraepithelial neoplasia (VIN), a precancerous condition that may progress to vulval cancer (79). A small randomized trial in 12 women with VIN found that supplementation with 200 mg/day or 400 mg/day of I3C for six months improved overall symptoms, as well as lesion size and appearance (80). Additional trials are necessary to determine whether I3C might be an effective treatment for VIN.

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a rare disease of children and adults, characterized by generally benign growths (papillomas) in the respiratory tract, which are caused by HPV infection (81). These papillomas occur most commonly on or around the vocal cords in the larynx (voice box), but they may also affect the trachea, bronchi, and lungs. The most common treatment for RRP is surgical removal of the papillomas. Since papillomas often recur, adjunct treatments may be used to help prevent or reduce recurrences (82). In immune-compromised mice transplanted with HPV-infected laryngeal tissue, only 25% of the mice fed I3C developed laryngeal papillomas compared to 100% of the control mice (83). In a small observational study of RRP patients, increased ratios of urinary 2HE$_1$:16HE$_1$ resulting from increased cruciferous vegetable consumption were associated with less severe RRP (84). In an uncontrolled pilot study, the effect of daily I3C supplementation (400 mg/day for adults and 10 mg/kg daily for children) on papilloma recurrence has been examined in RRP patients (85). Over a five-year follow-up period, 11 of the original 49 patients experienced no recurrence, 10 experienced a reduction in the rate of recurrence, 12 experienced no improvement, and 12 were lost to follow-up (86). I3C given for 6 months to 3 years to five children with an aggressive form of the disease halted the growth of the papillomas in three children after two years of treatment (87). In some patients, I3C may be an effective adjunct treatment to reduce the growth or recurrence of respiratory papillomas.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by chronic inflammation that may result in damage to the joints, skin, kidneys, heart, lungs, blood vessels, or brain (88). Estrogen is thought to play a role in the pathology of SLE because the disorder is much more common in women than men, and its onset is most common during the reproductive years when endogenous estrogen levels are highest (89). The potential for I3C supplementation to shift endogenous estrogen metabolism toward the less estrogenic metabolite 2HE$_1$, and away from the highly estrogenic metabolite 16HE$_1$ (see Anti-estrogenic activities), led to interest in its use in SLE (35). In an animal model of SLE, I3C feeding decreased the severity of kidney disease and prolonged survival (90). A small uncontrolled trial of I3C supplementation (375 mg/day) in female SLE patients found that I3C supplementation increased urinary 2HE$_1$:16HE$_1$ ratios, but the trial found no significant change in SLE symptoms after three months (90). Controlled clinical trials are needed to determine whether I3C supplementation could have beneficial effects in SLE patients.

Sources

Food sources

Glucobrassicin, the glucosinolate precursor of I3C, is found in a number of cruciferous vegetables, including broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard greens, radish, rutabaga, and turnip (91, 92). Although glucosinolates are present in relatively high concentrations in cruciferous vegetables, glucobrassicin makes up only about 8%-12% of the total glucosinolates (93). Total glucosinolate contents of selected cruciferous vegetables are presented in **Table 1**. However, the amount of total glucosinolates and the amount of indole-3-carbinol formed from glucobrassicin in food is variable and depends, in part, on the processing and preparation of foods (for more detailed information, see the article on Cruciferous Vegetables).

Table 1. Glucosinolate Content of Selected Cruciferous Vegetables (94)

Food (raw)	Serving	Total Glucosinolates (mg)
Brussels sprouts	½ cup	104
Garden cress	½ cup	98
Mustard greens	½ cup, chopped	79
Kale	1 cup, chopped	67
Turnip	½ cup, cubes	60
Cabbage, savoy	½ cup, chopped	35
Watercress	1 cup, chopped	32
Kohlrabi	½ cup, chopped	31
Cabbage, red	½ cup, chopped	29
Broccoli	½ cup, chopped	27
Horseradish	1 tablespoon (15 g)	24
Cauliflower	½ cup, chopped	22
Bok choi (pak choi)	½ cup, chopped	19

Supplements

Indole-3-Carbinol (I3C)

I3C is available without a prescription as a dietary supplement, alone or in combination products. Dosage ranges between 200 mg/day and 800 mg/day (95). I3C supplementation increased urinary 2HE$_1$ concentrations in adults at doses of 300 to 400 mg/day (39). I3C doses of 200 mg/day or 400 mg/day improved the regression of cervical intraepithelial neoplasia (CIN) in a preliminary clinical trial (75). I3C in doses up to 400 mg/day has been used to treat recurrent respiratory papillomatosis (see Disease Treatment) (85, 86).

3,3'-Diindolylmethane (DIM)

DIM is available without a prescription as a dietary supplement, alone or in combination products. In a small clinical trial, DIM supplementation at a dose of 108 mg/day for 30 days increased urinary 2HE$_1$ excretion in postmenopausal women with a history of breast cancer (34).

Safety

Adverse effects

Slight increases in the serum concentrations of the liver enzyme, alanine aminotransferase (ALT) were observed in two women who took unspecified doses of I3C supplements for four weeks (39). One person reported a skin rash while taking 375 mg/day of I3C (35). High doses of I3C (800 mg/day) have been associated with symptoms of disequilibrium and tremor, which resolved when the dose was decreased (85). In a phase I study in women at high risk for breast cancer, 5 out of 20 participants had gastrointestinal symptoms with single doses ≥600 mg, although others had no adverse effects with single doses up to 1,200 mg (6). No adverse effects were reported with daily consumption of 400 mg of I3C for four weeks (6).

In some animal models, I3C supplementation was found to enhance carcinogen-induced cancer development when given chronically after the carcinogen (96-99). When administered before or at the same time as the carcinogen, oral I3C inhibited tumorigenesis in animal models of cancers of the mammary gland (100, 101), uterus (102), stomach (103), colon (104, 105), lung (106), and liver (107, 108). Although the long-term effects of I3C supplementation on cancer risk in humans are not known, the contradictory results of animal studies have led several experts to caution against the widespread use of I3C and DIM supplements in humans until their potential risks and benefits are better understood (99, 109, 110).

Pregnancy and lactation

The safety of I3C or DIM supplements during pregnancy or lactation has not been established (95).

Drug interactions

No drug interactions with I3C or DIM supplementation in humans have been reported. However, preliminary evidence that I3C and DIM can increase the activity of CYP1A2 (111, 112) suggests the potential for I3C or DIM supplementation to decrease serum concentrations of medications metabolized by CYP1A2 (113). Both I3C and DIM modestly increase the activity of CYP3A4 in rats when administered chronically (114). This observation raises the potential for adverse drug interactions in humans since CYP3A4 is involved in the metabolism of approximately 60% of therapeutic drugs.

The acidic environment of the stomach allows I3C molecules to condense and generate a number of biologically active I3C oligomers (**Figure 2**). Drugs that block the production of stomach acids, like antacids, Histamine$_2$ (H$_2$) receptor antagonists, and proton-pump inhibitors, would likely prevent the generation of DIM and ICZ. However, it is not known whether these drugs limit the biological activities attributed to I3C and its derivatives (95).

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Isothiocyanates

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Summary

- Isothiocyanates are derived from the hydrolysis of glucosinolates — sulfur-containing compounds found in cruciferous vegetables. *(More information)*
- Each glucosinolate forms a different isothiocyanate when hydrolyzed. For example, broccoli is a good source of glucoraphanin, the glucosinolate precursor of sulforaphane, and sinigrin, the glucosinolate precursor of allyl isothiocyanate. *(More information)*
- Absorbed isothiocyanates are rapidly conjugated to glutathione in the liver, and then sequentially metabolized in the mercapturic acid pathway, before being excreted in the urine. *(More information)*
- Isothiocyanates may modulate the expression and activity of biotransformation enzymes that are involved in the metabolism and elimination of xenobiotics (e.g., carcinogens) from the body. In cultured cells and animal models, isothiocyanates also exhibited antioxidant and anti-inflammatory activities and interfered with numerous cancer-related targets and pathways. *(More information)*
- Although high intakes of cruciferous vegetables have been associated with a lower risk for cancer, there is insufficient evidence that exposure to isothiocyanates through cruciferous vegetable consumption decreases cancer risk. *(More information)*
- Glucosinolates are present in relatively high concentrations in cruciferous vegetables, but the amounts of isothiocyanates formed from glucosinolates in foods are variable and depend partly on food processing and preparation. *(More information)*

Introduction

Cruciferous vegetables, such as broccoli, cabbage, and kale, are rich sources of sulfur-containing compounds called glucosinolates (see the article on Cruciferous Vegetables). Isothiocyanates are biologically active hydrolysis (breakdown) products of glucosinolates. Cruciferous vegetables contain a variety of glucosinolates, each of which forms a different isothiocyanate when hydrolyzed (**Figure 1**) (1). For example, broccoli is a good source of glucoraphanin, the glucosinolate precursor of sulforaphane, and sinigrin, the glucosinolate precursor of allyl isothiocyanate (AITC) (see Food sources) (2). Watercress is a rich source of gluconasturtiin, the precursor of phenethyl isothiocyanate (PEITC), while garden cress is rich in glucotropaeolin, the precursor of benzyl isothiocyanate (BITC) (see Food sources). At present, scientists are interested in the cancer-preventive activities of vegetables that are rich in glucosinolates (see the article on Cruciferous Vegetables), as well as individual isothiocyanates (3).

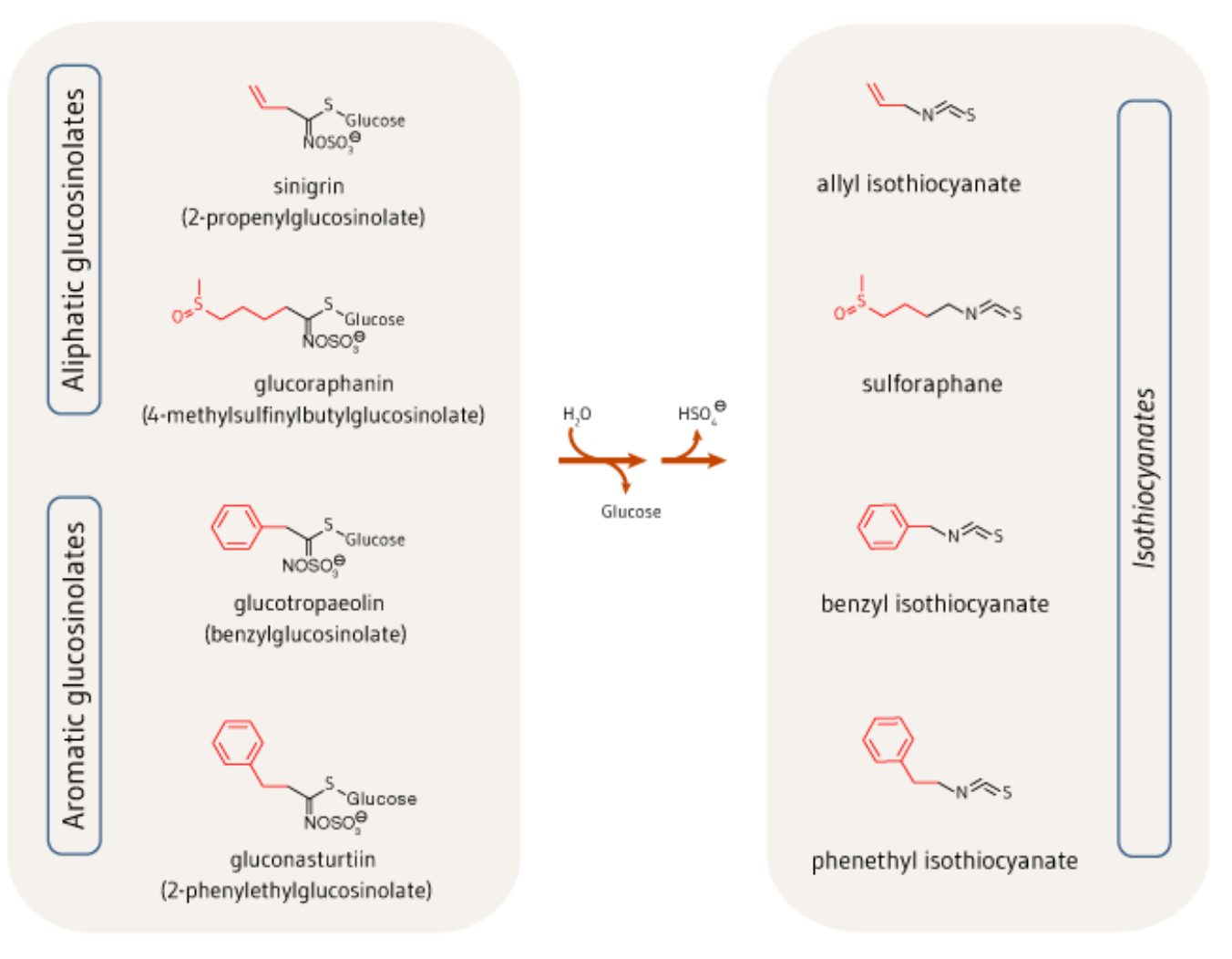
Metabolism and Bioavailability

Metabolism

The hydrolysis of glucosinolates, which is catalyzed by a class of enzymes called myrosinases (β-thioglucosidases), leads to the formation of breakdown compounds, such as thiocyanates, isothiocyanates, indoles, oxazolidine-2-thiones (e.g., goitrin), epithionitrile, and nitrile (see the article on Cruciferous Vegetables). In intact plant cells, myrosinase is physically separated from glucosinolates. Yet, when plant cells are damaged, myrosinase is released and comes in contact with glucosinolates, catalyzing their conversion into highly reactive metabolites that impart a pungent aroma and spicy (some say bitter) taste. Likewise, when raw cruciferous vegetables are chopped during the food preparation process, glucosinolates are rapidly hydrolyzed by myrosinase, generating metabolites that are then absorbed in the proximal intestine. In contrast, cooking cruciferous vegetables before consumption inactivates myrosinase, thus preventing the breakdown of glucosinolates. However, lightly cooking (i.e., light steam for <5 minutes) will preserve some of the myrosinase and allow for isothiocyanate conversion. A small fraction of intact glucosinolates may be absorbed in the small intestine, but a large proportion reaches the colon (4). In the colon, myrosinase produced by the microbiota can catalyze the generation of a wide range of metabolites from glucosinolates, depending on the pH and the presence of cofactors (4, 5).

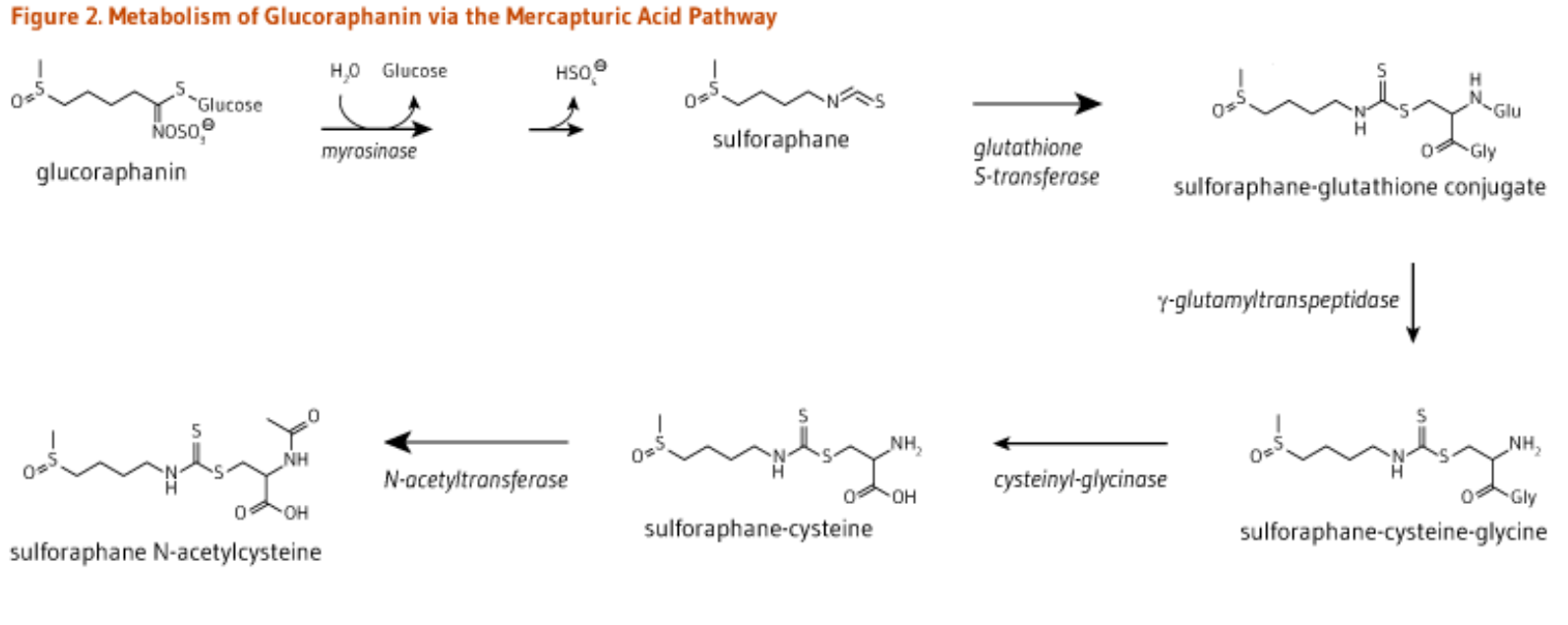
The hydrolysis of glucosinolates at neutral pH results in the formation of unique isothiocyanates (**Figure 1**). For example, sinigrin, glucoraphanin, glucotropaeolin, and gluconasturtiin are the glucosinolate precursors of AITC, sulforaphane, BITC, and PEITC, respectively (**Figure 1**). Once absorbed, glucosinolate-derived isothiocyanates (like sulforaphane) are promptly conjugated to glutathione by a class of phase II detoxification enzymes known as glutathione *S*-transferases (GSTs) in the liver, and then sequentially metabolized in the mercapturic acid pathway (**Figure 2**). This mechanism is meant to increase the solubility of isothiocyanates, thereby promoting a rapid excretion in the urine. Using sulforaphane as the model isothiocyanate, it has indeed been established that its metabolites — sulforaphane-glutathione, sulforaphane-cysteine-glycine, sulforaphane-cysteine, and sulforaphane N-acetylcysteine — collectively known as dithiocarbamates (**Figure 2**), are ultimately excreted in the urine (4).

Figure 1. Chemical Structures of Some Glucosinolates and their Isothiocyanate Derivatives



[Figure 1 - Click to Enlarge]

Figure 2. Metabolism of Glucoraphanin via the Mercapturic Acid Pathway



[Figure 2 - Click to Enlarge]

Bioavailability

The composition and content of glucosinolates in cruciferous vegetables are relatively stable but depend on the genus and species and can vary with plant growing and post-harvest storage conditions and culinary processing (6, 7). Since most cruciferous vegetables are cooked prior to eating, bacterial myrosinase in the gut, rather than plant myrosinase, is responsible for the initial step in glucosinolate degradation (**Figure 2**). In a feeding study involving 45 healthy subjects, the mean conversion rate of glucosinolates (of which 85% was glucoraphanin) to dithiocarbamates over a 24-hour period was estimated to be around 12% with wide variations among participants (range, 1.1 to 40.7%) (6). In contrast, 70%-75% of ingested isothiocyanates were found to be metabolized to dithiocarbamates. Therefore, following the ingestion of cooked cruciferous vegetables, the conversion of glucosinolates into isothiocyanates by gut bacteria appears to be a limiting step in the generation of dithiocarbamates (6). However, differences in individuals' capacity to metabolize glucosinolates have not been linked to differences in gut microbiota composition (8).

Biological Activities

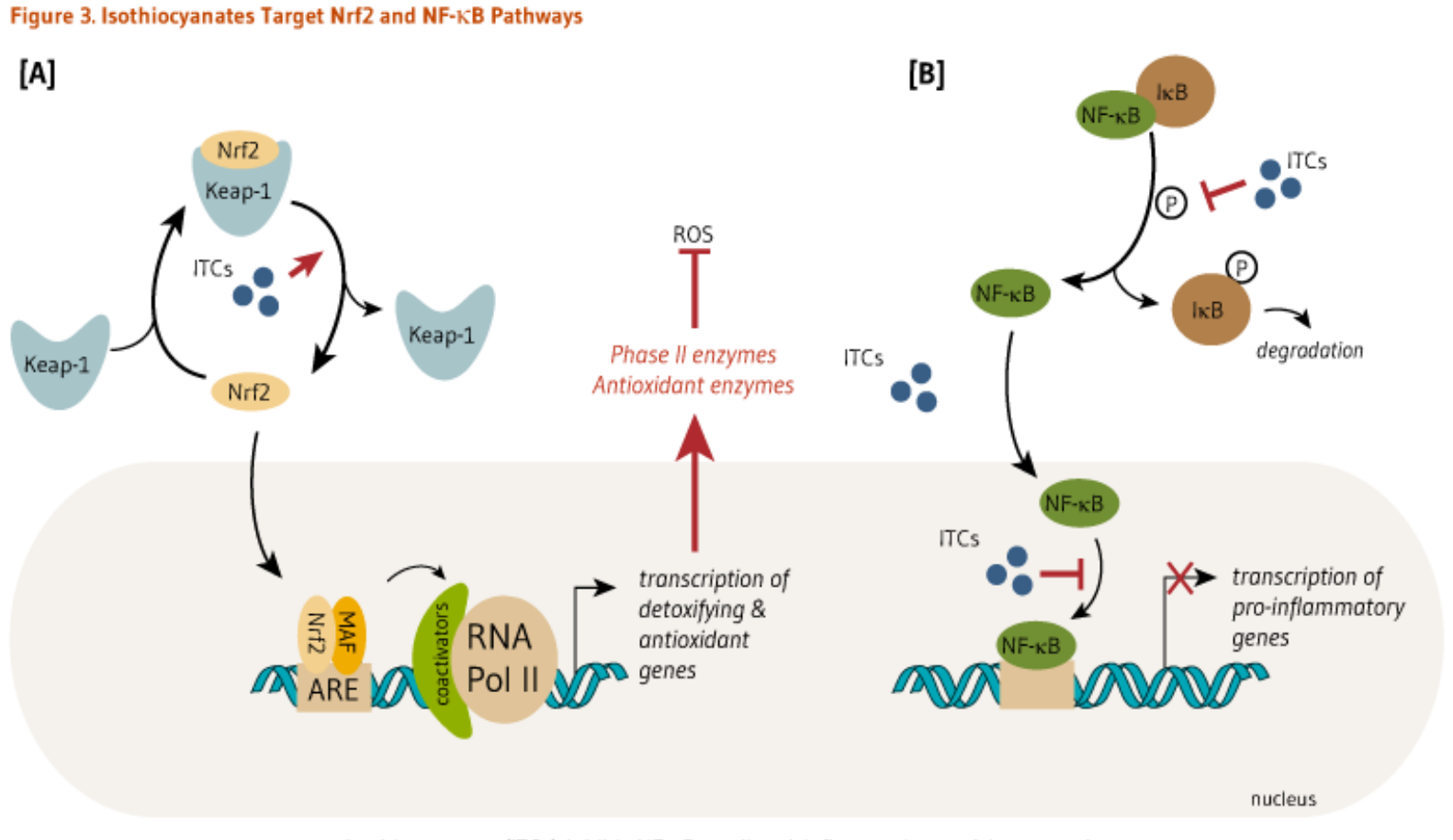
Antioxidant activity

Many isothiocyanates, particularly sulforaphane, have been shown to induce the expression of antioxidant enzymes via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway (9, 10). Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol (**Figure 3**). Keap1 responds to oxidative stress signals or chemical inducers by freeing Nrf2. Isothiocyanates can react with sulfhydryl residues of Keap1, causing the release of Nrf2. Nrf2 can then translocate to the nucleus and bind to the antioxidant response element (ARE) located in the promoters of genes coding for antioxidant/detoxifying enzymes and scavengers. Nrf2/ARE-dependent genes code for several mediators of the antioxidant response, including glutathione S-transferases (GSTs), thioredoxin, NAD(P)H quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) (11).

In numerous animal models, sulforaphane (often administered ip, iv, or sc, rather than po) was shown to exert protective effects on many tissues and organs by activating the Nrf2/ARE-dependent pathway (12). For example, sulforaphane reduced contrast agent-induced kidney damage in rats by increasing Nrf2 nuclear translocation and upregulating the expression of HO-1 and NQO-1 (13). Upregulation of the Nrf2 pathway by sulforaphane also attenuated oxidative damage-induced vascular endothelial cell injury in a mouse model of type 2 diabetes mellitus (14). In a rat model of hepatic ischemia reperfusion injury — whereby cellular damage is caused by the restoration of oxygen delivery to a hypoxic liver — pre-treatment with sulforaphane limited the reduction in glutathione (GSH) and the antioxidant enzymes, superoxide dismutase (SOD) and GSH peroxidase (GPx). Sulforaphane also upregulated the expression of Nrf2, NQO-1, and HO-1, and decreased ischemic death and apoptosis of liver cells (15).

Human studies are limited. In a placebo-controlled study, oral sulforaphane (in the form of broccoli sprout homogenate) increased the expression of NQO-1 and HO-1 in the upper airway within two hours of ingestion (16). Yet, in a recent trial in patients with chronic obstructive pulmonary disease (COPD), oral administration of sulforaphane for four weeks failed to induce the expression of Nrf2, NQO-1, and HO-1 in alveolar macrophages, bronchial epithelial cells, or peripheral blood mononuclear cells (17).

Figure 3. Isothiocyanates Target Nrf2 and NF-κB Pathways



Isothiocyanates (ITCs) inhibit NF-κB-mediated inflammation and increase the expression of phase II detoxifying/antioxidant enzymes via the Nrf2 signaling pathway. [A] ITCs induce the nuclear translocation of Nrf2 and increase the expression of Nrf2 target genes coding for phase II enzymes and antioxidant enzymes. [B] ITCs may prevent (1) the phosphorylation of NF-κB inhibitor, IκB; (2) the nuclear translocation of NF-κB; and (3) the transcriptional activity of NF-κB. *ARE, antioxidant response element; IκB, inhibitor of kappa B; Keap-1, Kelch-like ECH-associated protein 1; MAF, Nrf2 transcriptional cofactor; Nrf2, nuclear factor E2-related factor 2; NF-κB, nuclear factor kappa B; RNA Pol II, RNA polymerase II; ROS, reactive oxygen species.*

[Figure 3 - Click to Enlarge]

Anti-inflammatory activity

The therapeutic potential of sulforaphane has also been linked to its capacity to target pro-inflammatory pathways. Sulforaphane was found to attenuate pancreatic injury in a mouse model of acute pancreatitis by stimulating Nrf2-induced antioxidant enzymes (18). Concomitantly, sulforaphane significantly reduced the nuclear translocation of the pro-inflammatory transcription factor nuclear factor (NF)-κB in pancreatic acinar cells, downregulating the expression of NF-κB target genes that code for pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1β), and IL-6 (**Figure 3**) (18). Through inhibiting the NF-κB pathway, sulforaphane also targets other mediators of the inflammatory response, including the enzymes cyclooxygenase-2 (COX-2), prostaglandin E (PGE) synthase, and inducible nitric oxide synthase (iNOS). Sulforaphane exhibited anti-inflammatory effects in the lungs of mice with lipopolysaccharide (LPS)-induced acute respiratory distress syndrome (ARDS) by downregulating the expression of NF-κB, IL-6, TNF-α and COX-2, as well as decreasing production of nitric oxide (NO) and PGE2 (19). Other isothiocyanates have been shown to prevent the degradation of the NF-κB inhibitor, IκB, the nuclear translocation of NF-κB, and/or the transcriptional activity of NF-κB *in vitro* or in cultured cells (**Figure 3**) (20), which all can lead to a decrease in inflammatory responses.

The modulation of Nrf2 and NF-κB signaling pathways by isothiocyanates is especially relevant to the prevention of cancer because both oxidative stress and inflammation are significant contributors in the development and progression of cancer.

Anticancer activity

Biotransformation enzymes play important roles in the metabolism and elimination of a variety of chemicals, including drugs, toxins, and carcinogens. In general, phase I metabolizing enzymes catalyze reactions that increase the reactivity of hydrophobic (fat-soluble) compounds, preparing them for reactions catalyzed by phase II biotransformation enzymes. Reactions catalyzed by phase II enzymes generally increase water solubility and promote the elimination of the compound from the body (21).

Inhibition of phase I biotransformation enzymes

Isothiocyanates have been found to modulate the activity of phase I biotransformation enzymes, especially those of the cytochrome P450 (CYP) family. Using a primary rat hepatocyte-based model, both aliphatic (e.g., sulforaphane, AITC) and aromatic (e.g., BITC, PEITC) isothiocyanates (at 20-40 μM) have been found to downregulate CYP3A2 mRNA expression, as well as the activity of benzyloxyquinoline debenzylase, a marker of CYP3As (22). Aromatic isothiocyanates were also able to upregulate CYP1A1 and CYP1A2 mRNA expression and the activity of ethoxyresorufin-O-deethylase (EROD), a marker of CYP1A1/2 activities (22). In this model, sulforaphane inhibited EROD activity, yet failed to affect CYP1A1/2 mRNA expression (22). Using human liver microsomes, it was also recently reported that sulforaphane metabolites (0-200 μM) had little-to-no effect on the activities of CYP1A2, CYP2B6, CYP2D6, and CYP3A4 (23). The ability of PEITC to alter the expression and activity of CYP enzymes has been generally associated with a protective effect against (pro)carcinogen-induced tumor development in animal experiments (reviewed in 24). Increasing the activity of biotransformation enzymes may be beneficial if the elimination of potential carcinogens or toxins is enhanced. Yet, some procarcinogens require phase I enzymes in order to become active carcinogens capable of binding DNA and forming cancer-causing DNA adducts. Inhibition of specific CYP enzymes involved in carcinogen activation has been found to prevent the development of cancer in animal models (3).

Induction of phase II detoxifying enzymes

Many isothiocyanates are potent inducers of phase II detoxifying enzymes, including GSTs, UDP-glucuronosyl transferases (UGTs), NQO1, and glutamate cysteine ligase (GCL), that protect cells from DNA damage by carcinogens and reactive oxygen species (ROS) (25). The genes for these and other phase II enzymes contain AREs and are therefore under the control of Nrf2 (see Antioxidant activity). Limited data from clinical trials suggest that glucosinolate-rich foods can increase phase II enzyme activity in humans. When smokers consumed 170 g/day (6 oz/day) of watercress, urinary excretion of glucuronidated nicotine metabolites increased significantly, suggesting UGT activity increased (26). Brussels sprouts are rich in a number of glucosinolates, including precursors of AITC and sulforaphane. Consumption of 300 g/day (11 oz/day) of Brussels sprouts for one week significantly increased plasma and intestinal GST concentrations in nonsmoking men (27, 28).

Induction of cell cycle arrest and apoptosis

After a cell divides, it passes through a sequence of stages — collectively known as the cell cycle — before dividing again. Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or activation of pathways leading to programmed cell death (apoptosis) when the damage cannot be repaired (29). Defective cell cycle regulation and pro-survival mechanisms may result in the propagation of mutations that contribute to the development of cancer. Isothiocyanates have been found to modulate the expression of the cell cycle regulators, cyclins and cyclin-dependent kinases (CDK), as well as to trigger apoptosis in a number of cancer cell lines (20). In a mouse model of colorectal cancer, oral administration of PEITC reduced both the number and size of polyps; these changes were associated with activation of the CDK inhibitor, p21, inhibition of various cyclins (A, D1, and E), and induction of apoptosis (30). In a transgenic prostate adenocarcinoma mouse model, BITC limited the progress of prostatic intraepithelial neoplasia (PIN) to a well-differentiated carcinoma (31). This was related to a decreased expression of Ki67 (a marker of cell proliferation) and a downregulation of cyclin A, cyclin D1, and CDK2, which regulate cell cycle progression (31).

Inhibition of cell migration and invasion

The epithelial-to-mesenchymal transition (EMT) describes a process of epithelial cell transformation whereby cells lose their polarity and adhesion properties while gaining migratory and invasive properties through the expression of mesenchymal genes. Inhibition of the EMT by sulforaphane in thyroid cancer cells has been associated with upregulation of an epithelial marker, E-cadherin, and downregulation of a transcription factor (SNAI2), a filament protein (vimentin), and various enzymes (matrix metalloprotein [MMP]-2 and MMP-9) known to contribute to EMT and promote migration (32). In a xenograft mouse model of breast cancer, BITC inhibited high fat diet-driven promotion of breast tumor growth, as well as lung and liver metastasis (33). This study suggested that BITC might prevent the infiltration of macrophages in the tumor environment (33). In another model of breast tumor metastasis, PEITC inhibited the migration of tumor cells to the brain after injection into the heart of mice, limiting the growth of metastatic brain tumors (34).

Inhibition of angiogenesis

To fuel their rapid growth, invasive tumors must also develop new capillaries from preexisting blood vessels by a process known as angiogenesis. Isothiocyanates have been shown to prevent the formation of capillary-like structures from human umbilical endothelial cells (reviewed in 35). Isothiocyanates likely inhibit the expression and function of hypoxia inducible factors (HIFs) that control angiogenesis, as reported in endothelial cells and malignant cell lines (35).

Epigenetic regulation of gene expression

In the nucleus of a cell, DNA is coiled around proteins called histones, thereby forming the chromatin. The N-terminal tails of histones are targets for multiple modifications, including phosphorylation, methylation, acetylation, ubiquitination, poly ADP ribosylation, and sumoylation. Histone modification patterns have differential effects on chromatin structure, and, in synergy with DNA methylation, are implicated in the regulating expression of the genome (36). Within gene regulatory regions, the acetylation of lysine residues of histone tails has been correlated with activation of transcription. Conversely, the deacetylation of histones by histone deacetylases (HDAC) restricts access of transcription factors to the DNA and suppresses transcription. Because abnormal epigenetic marks disrupt the expression of specific tumor suppressor genes in cancer cells, compounds that re-induce their transcription, like those inhibiting HDACs, can potentially promote differentiation and apoptosis in transformed (precancerous) cells (37).

Isothiocyanates have been found to inhibit HDAC expression and/or activity in cultured cancer cells (38-43). Moreover, *in vivo* evidence for HDAC inhibition by sulforaphane came from a mouse model using prostate cancer xenografts (44). In humans, HDAC activity was reduced in blood cells following ingestion of 68 g (one cup) of sulforaphane-rich broccoli sprouts (44). Isothiocyanates may also affect microRNA-mediated gene silencing. In bladder cancer cells, E-cadherin induction by sulforaphane was partly due to the upregulation of miR-200c expression resulting in the miR-200c-dependent suppression of ZEB-1, a transcriptional repressor of E-cadherin (45). PEITC inhibited androgen receptor (AR) transcriptional activity in prostate cancer cells by repressing miR-141 expression and miR-141-mediated downregulation of small heterodimer partner (shp), a repressor of AR (46).

Antibacterial activity

Bacterial infection with *Helicobacter pylori* is associated with a marked increase in the risk of peptic ulcer disease and gastric cancer (47). In the test tube and in tissue culture, purified sulforaphane inhibited the growth and killed multiple strains of *H. pylori*, including antibiotic resistant strains (48). In an animal model of *H. pylori* infection, sulforaphane administration for five days eradicated *H. pylori* from 8 out of 11 xenografts of human gastric tissue implanted in immune-compromised mice (49). In another *H. pylori*-infected mouse model, a functional Nrf2 pathway was found to be required for the reduction of gastric inflammation and infection in mice fed broccoli sprouts (50). In a small clinical trial, consumption of up to 56 g/day (2 oz/day) of glucoraphanin-rich broccoli sprouts for one week was associated with *H. pylori* eradication in only three out of nine gastritis patients (51). In another trial, daily consumption of 70 g/day (~2-3 servings/day) of glucoraphanin-rich broccoli sprouts for two months significantly reduced markers of inflammation and infection in *H. pylori*–infected volunteers compared to those who consumed alfalfa sprouts (50). However, the extent to which glucoraphanin was converted to sulforaphane in broccoli sprout-fed participants was not measured.

Disease Prevention

Cancer

Isothiocyanates are thought to play a prominent role in the potential anticancer and cardiovascular benefits associated with cruciferous vegetable consumption (52, 53). Genetic variations in the sequence of genes coding for GSTs may affect the activity of GSTs. Such variations have been identified in humans. Specifically, null variants of the *GSTM1* and *GSTT1* alleles contain large deletions, and individuals who inherit two copies of the *GSTM1*-null or *GSTT1*-null alleles cannot produce the corresponding GST enzymes (54). It has been proposed that a reduced GST activity in these individuals would slow the rate of excretion of isothiocyanates, thereby increasing tissue exposure to isothiocyanates after cruciferous vegetable consumption (55). In addition, GSTs are involved in "detoxifying" potentially harmful substances like carcinogens, suggesting that individuals with reduced GST activity might also be more susceptible to cancer (56-58). Further, induction of the expression and activity of GSTs and other phase II detoxification/antioxidant enzymes by isothiocyanates is an important defense mechanism against oxidative stress and damage associated with the development of diseases like cancer and cardiovascular disease (11). The ability of glucoraphanin-derived sulforaphane to reduce oxidative stress in different settings is linked to activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway (see Biological Activities). Yet, whether potential protection conferred by isothiocyanates via the Nrf2-dependent pathway is diminished in individuals carrying *GST* null variants is currently unknown. Some, but not all, observational studies have suggested that GST genotypes could influence the associations between cruciferous vegetable consumption and risk of disease (59).

Naturally occurring isothiocyanates and their metabolites have been found to inhibit the development of chemically-induced cancers of the lung, liver, esophagus, stomach, small intestine, colon, and breast in a variety of animal models (20). Although observational studies provide some evidence that higher intakes of cruciferous vegetables are associated with decreased cancer risk in humans (59), it is difficult to determine whether such protective effects are related to isothiocyanates or other factors associated with cruciferous vegetable consumption (see the article on Cruciferous Vegetables). Clinical evidence of a protective effect of isothiocyanates in humans is scarce. For example, in a recent randomized, cross-over intervention, administration of PEITC (40 mg/day for five days) caused a modest, yet significant, 7.7% reduction in the metabolic activation of the tobacco-specific lung carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, in cigarette smokers (60). Another randomized controlled trial in men with biochemically relapsing cancer after radical prostatectomy suggested that prostate-specific antigen (PSA) values tended to increase less in those given daily oral sulforaphane (4.4 or 26.6 mg/day) for six months compared to those receiving the placebo (61). In a recent double-blind, randomized, placebo-controlled trial in women with abnormal mammograms, two-to-eight week consumption of about 250 mg/day of broccoli seed extract (~220 mg of glucoraphanin/day) before surgery failed to affect the expression of markers of proliferation and gene expression, including ki-67, p21, HDACs, and acetylated histones, in breast tissues collected after surgery (62).

Sources

Food sources

Cruciferous vegetables

Cruciferous vegetables, such as bok choi, broccoli, Brussels sprouts, cabbage, cauliflower, horseradish, kale, kohlrabi, mustard, radish, rutabaga, turnip, and watercress, are rich sources of glucosinolate precursors of isothiocyanates (63). Unlike some other phytochemicals, glucosinolates are present in relatively high concentrations in commonly consumed portions of cruciferous vegetables. For example one-half cup of raw broccoli might provide more than 25 mg of total glucosinolates. The glucosinolate content of selected cruciferous vegetables is presented in **Table 1** (64). Note that while the composition and content of glucosinolates in cruciferous vegetables are relatively stable, they depend on the genus and species and can vary greatly with plant growing and post-harvest storage conditions, as well as culinary processing.

Table 1. Glucosinolate Content of Selected Cruciferous Vegetables

Food (raw)	Serving	Total Glucosinolates (mg)
Brussels sprouts	½ cup (44 g)	104
Garden cress	½ cup (25 g)	98
Mustard greens	½ cup, chopped (28 g)	79
Turnip	½ cup, cubes (65 g)	60
Cabbage, savoy	½ cup, chopped (45 g)	35
Kale	1 cup, chopped (67 g)	67
Watercress	1 cup, chopped (34 g)	32
Kohlrabi	½ cup, chopped (67 g)	31
Cabbage, red	½ cup, chopped (45 g)	29
Broccoli	½ cup, chopped (44 g)	27
Horseradish	1 tablespoon (15 g)	24
Cauliflower	½ cup, chopped (50 g)	22
Bok choy (pak choi)	½ cup, chopped (35 g)	19

Table 2 lists vegetables that are relatively good sources of some of the isothiocyanates that are currently being studied for their potential anticancer properties (65).

Table 2. Food Sources of Selected Isothiocyanates and Their Glucosinolate Precursors

Isothiocyanate	Glucosinolate (precursor)	Food Sources
Allyl isothiocyanate (AITC)	Sinigrin	Broccoli, Brussels sprouts, cabbage, horseradish, kohlrabi, mustard, radish
Benzyl isothiocyanate (BITC)	Glucotropaeolin	Cabbage, garden cress, Indian cress
Phenethyl isothiocyanate (PEITC)	Gluconasturtiin	Watercress
Sulforaphane	Glucoraphanin	Broccoli, Brussels sprouts, cabbage, cauliflower, kale

Amounts of isothiocyanates formed from glucosinolates in foods are variable and depend partly on food processing and preparation (see the article on Cruciferous Vegetables). In a recent study that examined total isothiocyanate content in 73 samples from nine types of raw cruciferous vegetables commonly consumed in the US (namely broccoli, cabbage, cauliflower, Brussels sprout, kale, collard green, mustard green, and turnip greens), an average yield of 16.2 μmol/100 g wet weight was reported, with a 41-fold difference of isothiocyanate yield across the vegetables. The lowest mean level of isothiocyanate yield was found with raw cauliflower (1.5 μmol/100 g), while raw mustard greens had the highest yield (61.3 μmol/100g) (66).

Broccoli sprouts

The amount of glucoraphanin, the precursor of sulforaphane, in broccoli seeds remains more or less constant as those seeds germinate and grow into mature plants. Thus, three-day old broccoli sprouts are concentrated sources of glucoraphanin, which contain 10 to 100 times more glucoraphanin by weight than mature broccoli plants (67). Broccoli sprouts that are certified to contain at least 73 mg of glucoraphanin (also called sulforaphane glucosinolate) per 1-oz serving are available in some health food and grocery stores.

Supplements

Dietary supplements containing extracts of broccoli sprouts, broccoli, and other cruciferous vegetables are available without a prescription. Some products are standardized to contain a minimum amount of glucosinolates and/or sulforaphane. However, the bioavailability of isothiocyanates was found to be much lower with the consumption of broccoli supplements devoid of myrosinase than with the consumption of fresh broccoli sprouts. Peak concentrations of sulforaphane metabolites were found to be eight- and five-times greater in plasma and urine, respectively, following fresh broccoli versus supplement consumption (68). Interestingly, total HDAC activity in peripheral blood mononuclear cells (PBMC) of broccoli sprout consumers was reported to be significantly lower than in PBMC of subjects who consumed the supplement (see Biological Activities) (69).

Safety

Adverse effects

No serious adverse effects of isothiocyanates in humans have been reported. The majority of animal studies have found that isothiocyanates inhibited the development of cancer when given prior to the chemical carcinogen (pre-initiation). However, very high intakes of PEITC or BITC (25 to 250 times higher than average human dietary isothiocyanate intakes) have been found to promote bladder cancer in rats when given after cancer initiation by a chemical carcinogen (70). The relevance of these findings to human urinary bladder cancer is not clear, since at least one prospective cohort study found cruciferous vegetable consumption to be inversely associated with the risk of bladder cancer in men (71). Other potential toxic effects reported in rodents have not been corroborated by observations in humans (20).

Pregnancy and lactation

Although high dietary intakes of glucosinolates from cruciferous vegetables are not known to have adverse effects during pregnancy or lactation, there is no information on the safety of purified isothiocyanates or supplements containing high doses of glucosinolates and/or isothiocyanates during pregnancy or lactation in humans.

Drug interactions

Isothiocyanates are not known to interact with any drugs or medications. However, the potential for isothiocyanates to inhibit various isoforms of the cytochrome P450 (CYP) family of enzymes raises the potential for interactions with drugs that are CYP substrates (see Biological Activities). Isothiocyanates may sensitize cancer cells to anticancer drugs and/or increase drug cytotoxicity, as shown in *in vitro* and animal models. Yet, these potential benefits of isothiocyanates in cancer therapy have not been explored in clinical trials (72).

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Lignans

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Summary

- Lignans are polyphenolic compounds found in plants. *(More information)*
- Lignan precursors are found in a wide variety of plant-based foods, including seeds, whole grains, legumes, fruit, and vegetables. *(More information)*
- Flaxseeds are the richest dietary source of lignan precursors. *(More information)*
- When consumed, lignan precursors may be converted to the enterolignans, enterodiol and enterolactone, by bacteria that normally colonize the human intestine. *(More information)*
- Enterodiol and enterolactone have weak estrogenic activity but may also exert biological effects through non-estrogenic mechanisms. *(More information)*
- Lignan-rich foods are part of a healthy diet, but the roles of lignans in the prevention of hormone-associated cancers, osteoporosis, and cardiovascular disease are not yet clear. *(More information)*

Introduction

The enterolignans, enterodiol and enterolactone (**Figure 1**), are formed by the action of intestinal bacteria on lignan precursors found in plants (1). Because enterodiol and enterolactone can mimic some of the effects of estrogens, their plant-derived precursors are classified as phytoestrogens. Lignan precursors that have been identified in the human diet include pinoresinol, lariciresinol, secoisolariciresinol, matairesinol, and others (**Figure 2**). Secoisolariciresinol and matairesinol were among the first lignan precursors identified in the human diet and are therefore the most extensively studied. Lignan precursors are found in a wide variety of foods, including flaxseeds, sesame seeds, legumes, whole grains, fruit, and vegetables. While most research on phytoestrogen-rich diets has focused on soy isoflavones, lignans are the principal source of dietary phytoestrogens in the typical Western diet (2, 3).

Figure 1. Chemical Structures of the Enterolignans, Enterodiol and Enterolactone

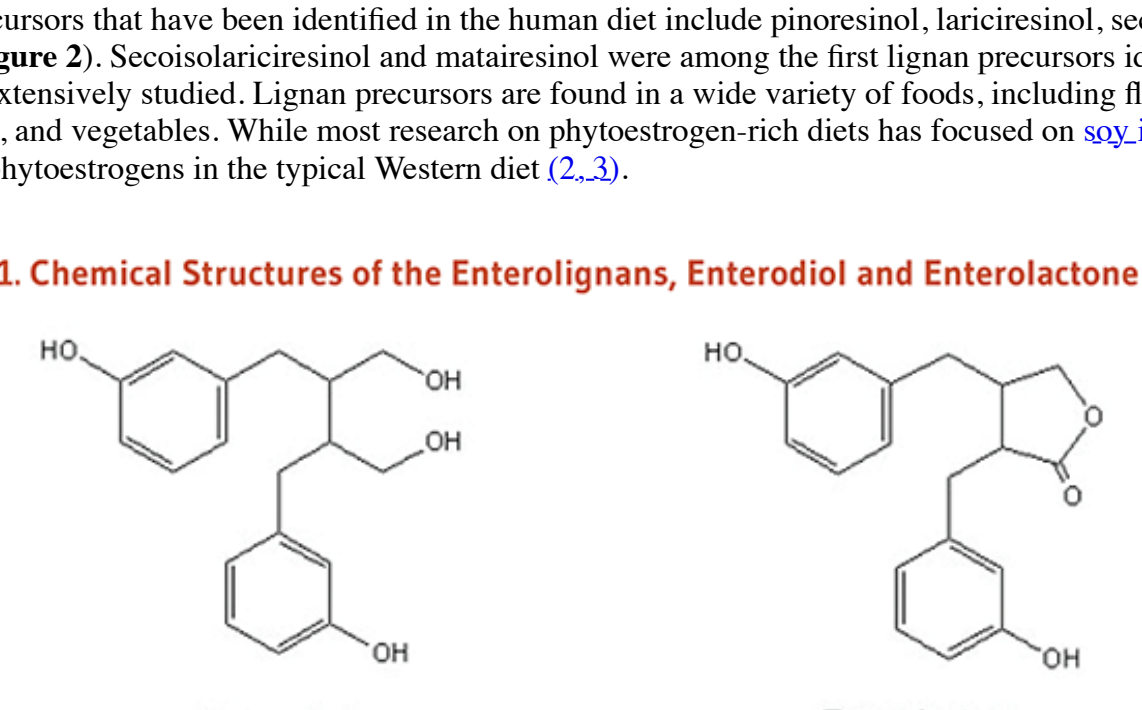
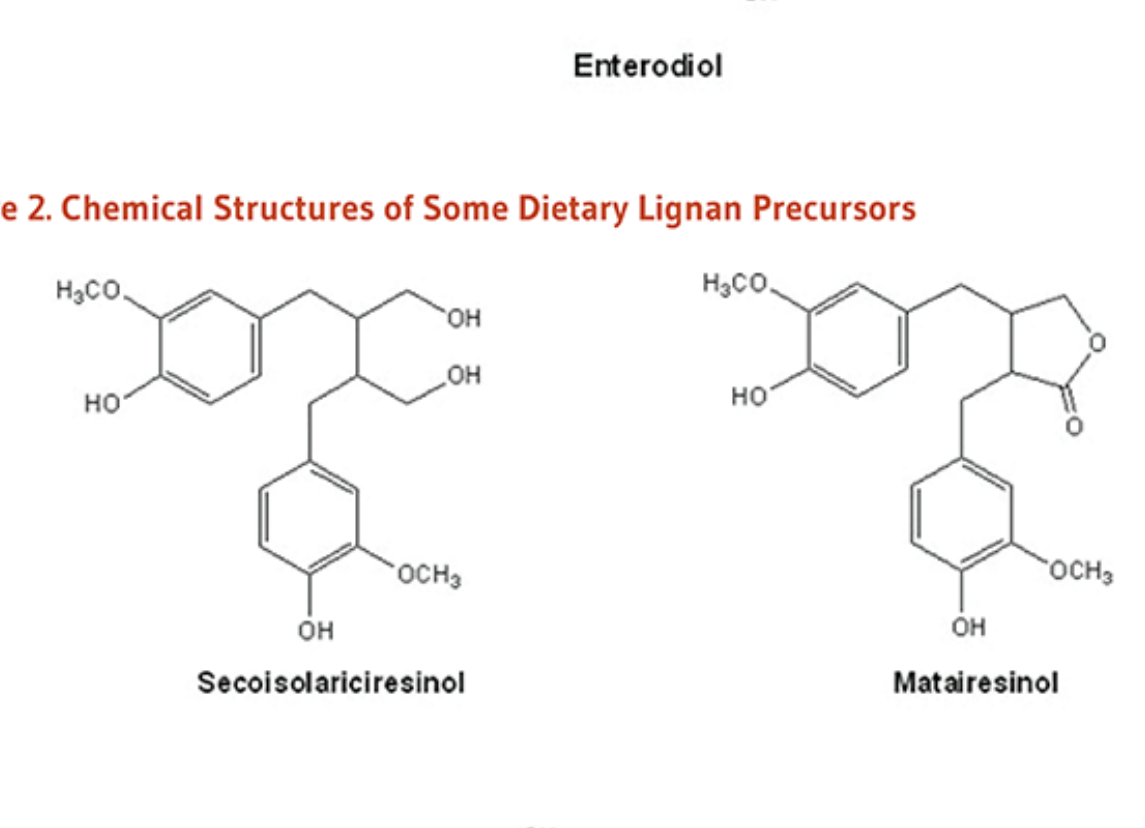


Figure 2. Chemical Structures of Some Dietary Lignan Precursors



Metabolism and Bioavailability

When plant lignans are ingested, they can be metabolized by intestinal bacteria to the enterolignans, enterodiol and enterolactone, in the intestinal lumen and then absorbed into the bloodstream (4). Enterodiol can also be converted to enterolactone by intestinal bacteria. Thus, enterolactone levels measured in blood and urine reflect the activity of intestinal bacteria in addition to dietary intake of plant lignans. Not surprisingly, antibiotic use has been associated with lower serum enterolactone concentrations (5).

Because data on the lignan content of foods are limited, blood and urinary enterolactone levels are sometimes used as markers of dietary lignan intake. A pharmacokinetic study that measured plasma and urinary levels of enterodiol and enterolactone after a single dose (0.9 mg/kg of body weight) of secoisolariciresinol, the principal lignan in flaxseed, found that at least 40% was available to the body as enterodiol and enterolactone (6). Plasma enterodiol concentrations peaked at 73 nanomoles/liter (nmol/L) an average of 15 hours after ingestion of secoisolariciresinol, and plasma enterolactone concentrations peaked at 56 nmol/L an average of 20 hours after ingestion. Thus, substantial amounts of ingested plant lignans are available to humans in the form of enterodiol and enterolactone.

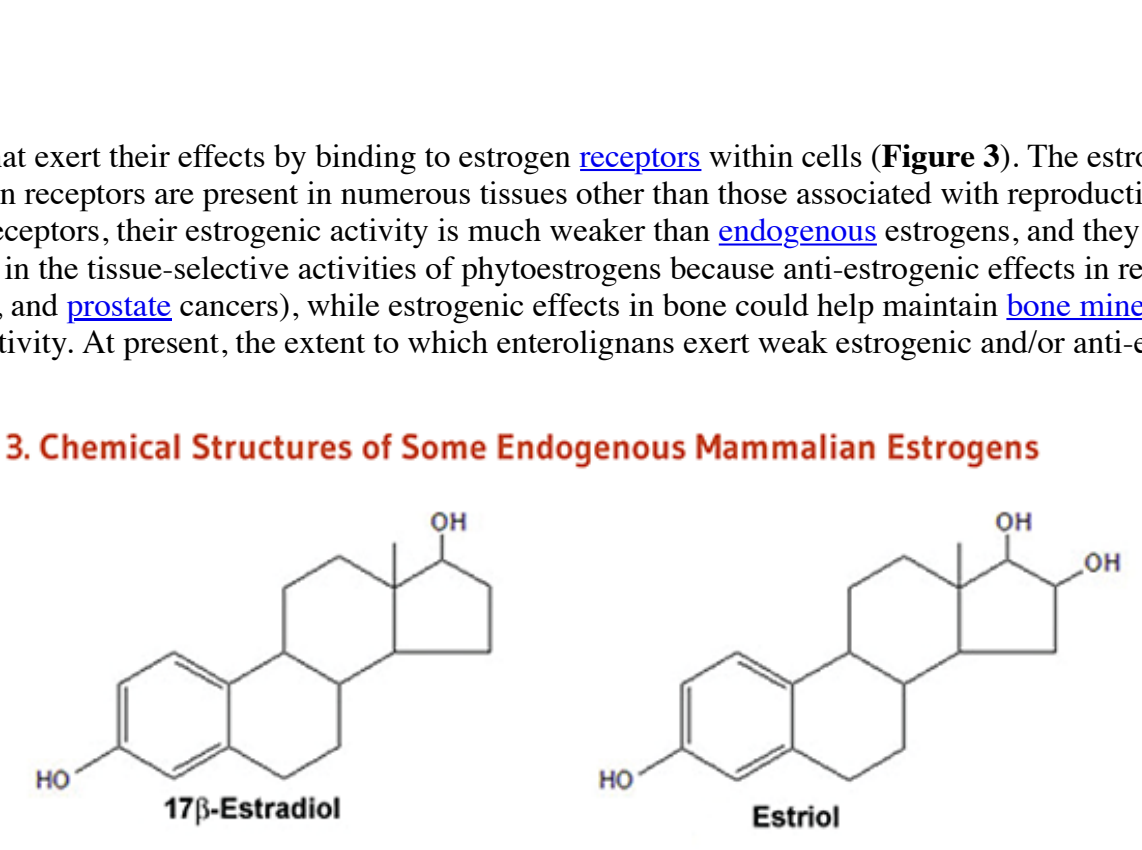
Considerable variation among individuals in urinary and serum enterodiol:enterolactone ratios has been observed in flaxseed feeding studies, suggesting that some individuals convert most enterodiol to enterolactone, while others convert relatively little (1). Individual differences in the metabolism of lignans, likely due to differing composition and activities of gut microbes, can influence the biological activities and health effects of these compounds (7). Several other factors, including antibiotic use, age, BMI, and smoking, may also help explain the variation of circulating enterolignan concentrations among individuals (7); these and other potential confounding factors should be controlled for in observational studies.

Biological Activities

Estrogenic and anti-estrogenic activities

Estrogens are signaling molecules (i.e., hormones) that exert their effects by binding to estrogen receptors within cells (**Figure 3**). The estrogen-receptor complex interacts with DNA to change the expression of estrogen-responsive genes. Estrogen receptors are present in numerous tissues other than those associated with reproduction, including bone, liver, heart, and brain (8). Although phytoestrogens can also bind to estrogen receptors, their estrogenic activity is much weaker than endogenous estrogens, and they may actually block or antagonize the effects of estrogen in some tissues (9). Scientists are interested in the tissue-selective activities of phytoestrogens because anti-estrogenic effects in reproductive tissue could help reduce the risk of hormone-associated cancers (breast, uterine, ovarian, and prostate cancers), while estrogenic effects in bone could help maintain bone mineral density. The enterolignans, enterodiol and enterolactone, are known to have weak estrogenic activity. At present, the extent to which enterolignans exert weak estrogenic and/or anti-estrogenic effects in humans is not well understood.

Figure 3. Chemical Structures of Some Endogenous Mammalian Estrogens



Estrogen receptor-independent activities

Enterolignans have biological activities that are unrelated to their interactions with estrogen receptors. By altering the activity of enzymes involved in estrogen metabolism, lignans may change the biological activity of endogenous estrogens (10). Lignans have also been shown to display antioxidant activity in laboratory studies (11), although the significance in humans is not entirely clear since lignans are rapidly and extensively metabolized. For example, a cross-sectional study found that a biomarker of oxidative damage was inversely associated with serum enterolactone concentrations in men (12), but this association could be due to enterolactone and/or other antioxidants present in lignan-rich foods. Moreover, enterolignans may have anti-inflammatory properties, as well as anti-proliferative and anticancer activities that are independent of estrogen signaling (13-15).

Disease Prevention

Cardiovascular disease

Diets rich in foods containing plant lignans (whole grains, nuts and seeds, legumes, and fruit and vegetables) have been consistently associated with reductions in risk of cardiovascular disease. However, it is likely that numerous nutrients and phytochemicals found in these foods contribute to their cardioprotection.

Higher dietary intakes of two lignans, matairesinol and secoisolariciresinol, were not linked to total cardiovascular disease in 16,162 middle-aged and older women participating in the Dutch PROSPECT European Prospective study Into Cancer and nutrition (EPIC) study (16). A large prospective cohort study conducted within Spain's PREDIMED trial — a trial evaluating the effects of a Mediterranean diet on cardiovascular disease outcomes — followed 7,172 older adults at high risk of cardiovascular disease for a mean of 4.3 years (17). In this study, the highest quintile of dietary lignan intake (mean intake, 0.94 mg/day), measured by a food frequency questionnaire at baseline, was associated with a 49% lower risk of incident cardiovascular disease compared to the lowest quintile (mean intake, 0.44 mg/day of lignans). The primary dietary source of lignans in this cohort was virgin olive oil (17), which itself is known to be cardioprotective.

Coronary heart disease

In a prospective, nested case-control study in 334 middle-aged Finnish men, followed for an average of 7.7 years, higher serum enterolactone concentrations (a marker of plant lignan intake) were associated with a lower risk of acute coronary events (18). A prospective cohort study of 1,889 Finnish men followed for an average of 12 years, found those with the highest serum enterolactone concentrations were significantly less likely to die from coronary heart disease (CHD) or cardiovascular disease than those with the lowest concentrations (19). However, a study in male smokers did not find strong support for an association between serum enterolactone concentration and CHD (20). Additionally, a nested case-control study in men and women residing in the Netherlands did not find association between plasma concentrations of enterolactone or enterodiol and nonfatal myocardial infarction (236 cases and 283 controls), although the study population was young (ages 20-59 at baseline) and followed for only a mean of 4.5 years (21). A 2017 meta-analysis of three of these studies found no association between blood enterolactone concentration and non-fatal myocardial infarction (22). Moreover, dietary lignan intake was not linked to coronary cardiovascular disease in women participating in the Dutch PROSPECT EPIC study (16).

Clinical trials of lignan supplementation would be needed to determine the effects of lignans on coronary heart disease.

Cardiovascular risk factors

Blood lipids. Flaxseeds are among the richest sources of plant lignans in the human diet, but they are also good sources of other nutrients and phytochemicals with cardioprotective effects, such as omega-3 fatty acids (i.e., α-linolenic acid) and fiber. Supplementation trials have generally used ground or milled flaxseed (i.e., flax meal), which has a higher bioavailability of enterolignans compared to whole flaxseed (23). Five small clinical trials found that adding 30 to 50 g/day of flaxseed to the usual diet for 4 to 12 weeks resulted in modest 8%-20% decreases in low-density lipoprotein (LDL-cholesterol concentration (24-28), but four other trials did not observe significant reductions in LDL-cholesterol after adding 30 to 40 g/day of flaxseed to the diet (29-32). A double-blind, randomized controlled trial in adults, ages 44 to 75 years, found that supplementation with 40 g/day of flaxseed led to significant reductions in LDL-cholesterol after five weeks, but the cholesterol reductions were not statistically significant following 10 weeks' supplementation (33). Additionally, a one-year clinical trial in postmenopausal women reported that supplementation with 40 g/day of flaxseed did not lower LDL-cholesterol compared to a placebo containing wheat germ (34). Most of these trials were in healthy participants free of cardiovascular disease. In a randomized, double-blind, placebo-controlled trial in 84 patients with peripheral artery disease, 30 g/day of flaxseed for 12 months did not reduce total or LDL-cholesterol compared to placebo, although cholesterol reductions within the flaxseed-supplemented group were evident at 1 month and 6 months compared to baseline but not at 12 months (35).

Any effect of flaxseed supplementation on blood lipids might be attributed to flaxseed constituents other than lignans (i.e., protein, fiber, omega-3 fatty acids, phytochemicals). At least two trials have investigated the effect of supplementation with isolated flaxseed lignan. In a randomized, double-blind, placebo-controlled cross-over trial in 22 healthy postmenopausal women, six-week supplementation with 500 mg/day of secoisolariciresinol diglucoside — derived from flaxseed — had no effect on LDL-cholesterol concentration or other measured blood lipids despite significant increases in serum enterolactone concentration (36). Additionally, a randomized, double-blind, placebo-controlled cross-over trial in 68 patients with type 2 diabetes and mild hypercholesterolemia found no effect of 360 mg/day of secoisolariciresinol diglucoside for 12 weeks on concentration of blood cholesterol or other blood lipids (37).

Large-scale supplementation trials with isolated lignans would be needed to determine whether lignans have cholesterol-lowering effects.

Blood pressure. A 2016 meta-analysis pooled the results of 15 randomized controlled trials, some in healthy participants and some in participants with chronic disease (i.e., type 2 diabetes, metabolic syndrome, peripheral arterial disease) or risk factors of cardiovascular disease. Supplementation with flaxseed was linked to a 2.9 mm Hg reduction in systolic blood pressure and a 2.4 mm Hg reduction in diastolic blood pressure; these blood pressure reductions were greater in trials of longer duration (≥12 weeks vs. <12 weeks; 38). Additionally, data stratification by supplement type revealed a benefit of supplemental flaxseed powder but not of lignan extracts containing 360 to 600 mg/day of secoisolariciresinol diglucoside (38), suggesting the non-lignan constituents of flaxseed may be responsible for any blood pressure-lowering effects.

Hormone-associated cancers

Breast cancer

Overall, there is limited evidence that dietary intake of plant lignans is associated with breast cancer risk; studies on the association have reported conflicting results. Two prospective cohort studies examining plant lignan intake and breast cancer found no association (39, 40). A more recent prospective study reported no association between total lignan intake and breast cancer in premenopausal women (41). In another prospective analysis, the same group of authors found postmenopausal women in the highest quartile of dietary lignan intake had a 17% lower risk of breast cancer compared to women in the lowest quartile, but this protective association was only observed in women with estrogen-positive and progesterone-positive tumors (42). A prospective cohort study of 51,823 postmenopausal Swedish women, followed for an average of 8.3 years, found that women in the highest quartile of lignan intake (≥1,036 mg/day) had a 17% lower risk of invasive breast tumors compared to those in the lowest quartile (lignan intake <712 mg/day) (43). In this study, a strong inverse association of lignan intake and breast cancer risk was observed in women who had used postmenopausal hormones at some point in their life, but no association was evident in those who had never used such hormones (43). A 2009 meta-analysis did not find an overall association between dietary lignan intake and breast cancer, but when the analysis was limited to postmenopausal women, the authors reported a 15% reduction in risk of breast cancer with high lignan intake (44). A similar result was found in a subsequent meta-analysis that included 11 prospective cohort and 10 case-control studies: no association of lignan intake and breast cancer was observed in women overall, but data stratification by menopausal status revealed that the highest lignan intakes were associated with a 14% lower risk of breast cancer among postmenopausal women (13 studies; 45).

Several studies, mainly case-control studies, have examined the relationship between blood or urine concentrations of enterolactone and breast cancer, reporting conflicting results (46-48). Two meta-analyses did not find an association between blood concentrations of enterolactone and breast cancer (44, 45).

At present, it is not clear whether high intakes of plant lignans or high circulating levels of enterolignans offer significant protection against breast cancer. Randomized controlled trials of lignan supplementation would be needed to address this question.

Endometrial and ovarian cancers

Overall, there is limited evidence that dietary lignan intake or circulating enterolignan concentration (a marker of lignan intake) is associated with endometrial cancer or ovarian cancer.

In a case-control study of lignans and endometrial cancer, US women with the highest intakes of plant lignans had the lowest risk of endometrial cancer, but the reduction in risk was statistically significant in postmenopausal women only (49). However, two population-based, case-control studies, one conducted in the US (50) and one in Australia (51), found dietary lignan intake was not linked to endometrial cancer. Moreover, a prospective case-control study in three different countries (US, Sweden, and Italy) did not find an association between circulating enterolactone and endometrial cancer in premenopausal or in postmenopausal women (52). A large case-cohort study among Danish women, ages 50-64 years, also reported no association of plasma enterolactone concentration and endometrial cancer (53).

In an early case-control study among US women ages 40 to 85 years, those with the highest combined intakes of the lignans, secoisolariciresinol and matairesinol, had the lowest risk of ovarian cancer — intakes greater than 708 mg/day of these lignans were associated with a 57% lower risk of ovarian cancer compared with intakes less than 304 mg/day (54). A case-control study in Australia reported no association of total dietary lignans and risk of ovarian cancer but found a significant, inverse association of matairesinol and lariciresinol, individually, with ovarian cancer (51). However, two other studies, a population-based case-control study in the US (55) and a prospective cohort study in Sweden (56) found no relationship between dietary lignan intake and ovarian cancer.

Although some of these studies support the hypothesis that diets rich in plant foods may be helpful in decreasing the risk of hormone-associated cancers, they do not provide strong evidence that lignans in particular are protective against endometrial or ovarian cancer.

Prostate cancer

Several observational studies have examined the association between dietary lignan intake or circulating enterolignan concentration (a marker of lignan intake) and prostate cancer, with most reporting no association. A meta-analysis of three studies (two population-based, case-control studies and one nested case-control study) found lignan intake was not linked to prostate cancer risk (57). Moreover, a meta-analysis of nested case-control studies did not find circulating concentration of enterolactone (total of 2,828 cases and 5,593 controls pooled from five studies) or enterodiol (total of 1,002 cases and 1,197 controls pooled from two studies) to be associated with prostate cancer (58). Yet another meta-analysis found no association between dietary lignan intake (total lignans, or matairesinol or secoisolariciresinol, separately) or circulating enterolactone concentration and prostate cancer risk (59). While adherence to a plant-based diet may be linked to a lower risk of prostate cancer (60), evidence that dietary lignans are protective is lacking.

Osteoporosis

Research on the effects of dietary lignan intake on osteoporosis risk is very limited. In a prospective cohort study of 2,580 postmenopausal women and 4,973 men enrolled in the European Prospective Investigation into Cancer (EPIC) study, dietary intake of matairesinol and secoisolariciresinol was not associated with bone density, when assessed by ultrasound of the heel bone (61). In two much smaller observational studies, urinary enterolactone excretion was used as a marker of dietary lignan intake. One study of 75 postmenopausal Korean women, who were classified as osteoporotic, osteopenic, or normal on the basis of bone mineral density (BMD) measurements, found that urinary enterolactone excretion was positively associated with BMD of the lumbar spine and hip (62). However, a study of 50 postmenopausal Dutch women found that higher levels of urinary enterolactone excretion were associated with higher rates of bone loss (63).

In two separate placebo controlled trials, supplementation of postmenopausal women with 25 to 40 g/day of ground flaxseed for three to four months did not significantly alter biochemical markers of bone formation or bone resorption (loss) (31, 64). In a placebo-controlled trial that included a daily walking intervention in both groups of older adults, supplementation with a flaxseed lignan complex (containing 543 mg/day of secoisolariciresinol) for six months had no effect on bone mineral density measured by DXA (65).

More research is necessary to determine whether high dietary intakes of plant lignans can decrease the risk or severity of osteoporosis.

Type 2 diabetes mellitus

More than 10% of the US population has type 2 diabetes mellitus and another 35% has impaired glucose control (prediabetes) that places them at high risk of developing type 2 diabetes (66). A number of dietary polyphenols found in plant-based foods may affect glucose metabolism and thus aid in the prevention or management of the condition. A few observational studies have examined the association of lignan intake and incidence of diabetes. A prospective cohort study in 6,547 Iranian adults, followed for a mean of 3.0 years, reported an inverse association between dietary lignan intake (measured by food frequency questionnaire) and incidence of type 2 diabetes (67). In particular, this study found the highest versus lowest quartile of lignan intake (median of 9.1 mg/day vs. 1.6 mg/day) to be associated with a 40% lower risk of type 2 diabetes (67). However, no association between lignan intake (highest vs. lowest quintile of intake, median of 2.3 mg/day vs. 0.6 mg/day) and type 2 diabetes was reported in a prospective, case-cohort study conducted in Europe that included more than 15,000 adults (EPIC-InterAct; 68).

Studies that utilize biomarkers of lignan intake, such as urinary concentrations of enterodiol or enterolactone, provide a more accurate estimate of lignan intake compared to self-reported questionnaires (69). A prospective, nested case-control study of two cohorts of US women participating in the Nurses' Health Study (NHSI with mean age of 66 years and NHSII with mean age of 45 years) found lower concentrations of enterodiol and enterolactone in diabetic case subjects than in controls (70). Upon adjustment for potential confounders, only higher concentrations of urinary enterolactone were associated with a lower risk of developing type 2 diabetes, and this was driven by a significant association in the younger cohort of women (70). A nested case-control study within men and women participating in the Singapore Chinese Health Study (mean age, 59.8 years) reported no association between urinary enterodiol or enterolactone and type 2 diabetes (71).

Because higher lignan intakes may be a marker of a healthy diet in general, randomized controlled trials of lignan supplementation in healthy individuals would inform whether lignans affect glucose homeostasis and risk of developing type 2 diabetes. Interestingly, an eight-week, double-blind, placebo-controlled trial in hypercholesterolemic individuals found that a flaxseed lignan extract containing 600 mg/day of secoisolariciresinol diglucoside decreased fasting glucose concentrations compared to placebo, and the effect was stronger in those with higher baseline glucose concentrations (72). Supplementation with an extract containing 300 mg/day of secoisolariciresinol diglucoside had no effect on fasting glucose concentrations (72).

Mortality

A few studies have examined whether dietary lignan intake is related to all-cause and cause-specific mortality. The European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain prospective cohort study investigated the relationship between lignan intake and all-cause mortality in 40,622 adults (ages 29-70 years) (73). After a mean follow-up of 13.6 years, dietary lignan intake was not associated with all-cause mortality (73). Additionally, dietary lignan intake was not linked to all-cause mortality in a much smaller study that followed 570 older Dutch men for 15 years (74). In this study, an inverse association was observed for intake of a specific lignan, matairesinol, with all-cause mortality and cardiovascular-related mortality, including death from coronary heart disease, although wine consumption modified these associations (74). However, an analysis of a 4.8-year trial that investigated the health effects of a Mediterranean diet in 7,172 older adults at high risk for cardiovascular disease (the PREDIMED trial in Spain) revealed that those in the highest quintile of lignan intake (mean of 0.94 mg/day) had a 40% lower risk of all-cause mortality compared to the lowest quintile (mean of 0.44 mg/day of lignans; 75). A 2017 meta-analysis found no association of lignan intake with all-cause mortality (3 studies mentioned above) or with mortality related to cardiovascular disease (2 studies; 76).

Other studies have assessed whether blood or urinary biomarkers of lignan intake are associated with mortality. In a prospective cohort study of 1,889 healthy, middle-aged Finnish men, followed for a mean of 12.2 years, the highest quartile of serum enterolactone concentration was associated with a 56% lower risk of coronary heart disease-related mortality and a 45% lower risk of cardiovascular disease-related mortality; no association of serum enterlactone and all-cause mortality was found in this study (19). However, serum enterolactone was not associated with coronary death in a case-cohort study in Finnish male smokers (20). In a national cross-sectional survey of US adults (NHANES 1999-2004), those in the highest tertile of urinary total enterolignan concentration had a lower risk of cardiovascular-related and all-cause mortality, and those with the highest urinary enterolactone concentrations had a significantly lower risk of all-cause mortality (77). These measures were not associated with mortality from cancer in this analysis, and urinary enterodiol concentration was not related to any of the mortality endpoints (77). A 2017 meta-analysis that combined results of these studies of lignan biomarkers found that enterolactone was inversely associated with both cardiovascular disease-related mortality and all-cause mortality (22). Most recently, a case-cohort study within the Danish Diet, Cancer and Health cohort found that higher pre-diagnostic plasma concentrations of enterolactone were linked to a lower risk of all-cause and diabetes-specific mortality among adults with type 2 diabetes (78).

Sources

Food sources

Lignans are present in a wide variety of plant foods, including seeds (flax, pumpkin, sunflower, poppy, sesame), whole grains (rye, oats, barley), bran (wheat, oat, rye), beans, fruit (particularly berries), vegetables, and beverages like tea, coffee, and wine (47, 79, 80). Secoisolariciresinol, matairesinol, pinoresinol, and lariciresinol contribute substantially to total dietary lignan intakes, although this varies with dietary pattern (80).

Flaxseed is by far the richest dietary source of plant lignans (81), and lignan bioavailability can be improved by crushing or milling flaxseed (23). Lignans are not associated with the oil fraction of foods, so flaxseed oils do not typically provide lignans unless ground flaxseed has been added to the oil. A variety of factors may affect the lignan content of plants, including geographic location, climate, maturity, and storage conditions. **Table 1** provides the total lignan (secoisolariciresinol, matairesinol, pinoresinol, and lariciresinol) content of selected lignan-rich foods (82). The Phenol-Explorer (version 3.6) database lists content of 25 different lignans in various foods.

Surveys have found median total lignan intake to be 0.98 mg/day in the Netherlands (83), 0.85 mg/day in Canada (84), and 0.76 mg/day in Spain (85). Plant lignans are the principal source of phytoestrogens in the diets of people who do not typically consume soy foods. The daily phytoestrogen intake of postmenopausal women in the US was estimated to be less than 1 mg/day, with 80% from lignans and 20% from isoflavones (86).

Table 1. Total Lignan Content of Selected Foods

Food	Serving	Total Lignans (mg)
Flaxseeds	1 oz	85.5
Sesame seeds	1 oz	11.2
Curly kale	½ cup, chopped	0.8
Broccoli	½ cup, chopped	0.6
Apricots	½ cup, sliced	0.4
Cabbage	½ cup, chopped	0.3
Brussels sprouts	½ cup, chopped	0.3
Strawberries	½ cup	0.2
Tofu	¼ block (4 oz)	0.2
Dark rye bread	1 slice	0.1

Supplements

Dietary supplements containing lignans derived from flaxseed are available in the US without a prescription (87); secoisolariciresinol is the primary lignan in such supplements (82).

Safety

Adverse effects

Lignan precursors in food are not known to have any serious adverse effects. Flaxseeds, which are rich in lignan precursors as well as dietary fiber, may increase stool frequency or cause diarrhea in doses of 45 to 50 g/day in adults (24, 88). One small, placebo-controlled study found that 50 mg/day of sesame lignans (1:1 mixture of sesamin and episesamin) for 28 days did not result in any serious adverse effects, although abdominal flatulence was associated with the sesame lignan supplementation (89). The safety of lignan supplements in pregnant or lactating women has not been established; therefore, lignan supplements should be avoided by women who are pregnant, breast-feeding, or trying to conceive.

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Phytosterols

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Summary

- Plant sterols and plant stanols, known commonly as phytosterols, are plant-derived compounds that are structurally related to cholesterol. *(More information)*
- Early human diets were likely rich in phytosterols, providing as much as 1 g/day; however, the typical Western diet today is relatively low in phytosterols. *(More information)*
- Although phytosterols are present in the diet in amounts similar to cholesterol, they are poorly absorbed and blood concentrations tend to be low. After absorption into enterocytes, phytosterols are actively excreted back into the intestinal lumen by the ATP-binding cassette transporter, ABCG5/G8. *(More information)*
- Phytosterols interfere with the intestinal absorption of dietary cholesterol by displacing cholesterol from micelles; they also facilitate the excretion of biliary cholesterol in the feces. *(More information)*
- Numerous clinical trials have demonstrated that daily consumption of phytosterols from phytosterol-enriched foods can significantly lower serum low-density lipoprotein (LDL)-cholesterol. An average phytosterol intake of 2 g/day lowers serum LDL-cholesterol by 8%-10%. *(More information)*
- The effect of long-term use of foods enriched with phytosterols on cardiovascular risk is not known. *(More information)*
- The results of a few clinical trials suggested that phytosterol supplementation at relatively low doses can improve urinary tract symptoms related to benign prostatic hyperplasia, but further research is needed to confirm these findings. *(More information)*
- Good food sources of phytosterols include unrefined vegetable oils, whole grains, nuts, seeds, and legumes. *(More information)*
- Foods and beverages with added phytosterols are now available in many countries throughout the world, and some countries allow health claims on such commercial products. *(More information)*
- Consumption of phytosterol-enriched foods may have undesirable effects, such as a reduction in plasma carotenoid concentrations. *(More information)*

Introduction

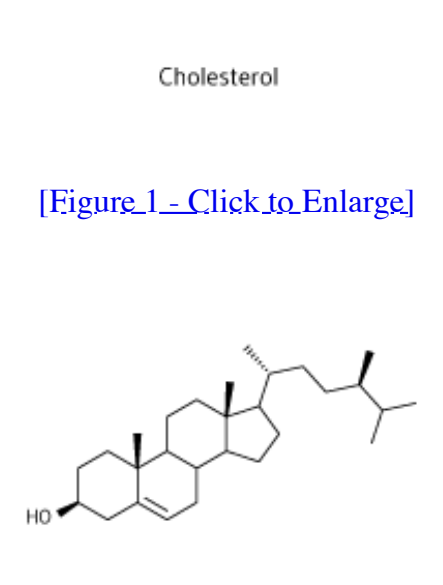
Throughout much of human evolution, it is likely that large amounts of plant foods were consumed (1). In addition to being rich in fiber and plant protein, the diets of our ancestors were also rich in phytosterols — plant-derived compounds that are structurally very similar to cholesterol (**Figure 1**). There is increasing evidence to suggest that the reintroduction of plant foods providing phytosterols into the modern diet could improve serum lipid (cholesterol) profiles and help reduce the risk of cardiovascular disease (1).

Cholesterol in human blood and tissues is derived from the diet, as well as from endogenous cholesterol synthesis. In contrast, all phytosterols in human blood and tissues are derived from the diet because humans cannot synthesize phytosterols (2). While cholesterol is the predominant sterol in animals, including humans, a variety of sterols are found in plants (3). Nutritionists recognize two classes of phytosterols:

(1) **Plant sterols** have a double bond in the sterol ring. The most abundant sterols in plants and the human diet are β-sitosterol, campesterol, and stigmasterol (**Figure 2**).

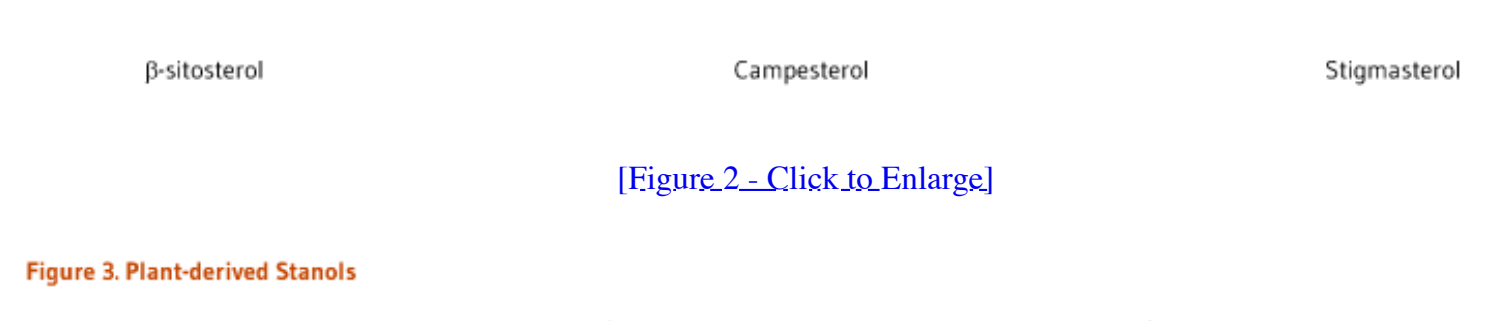
(2) **Plant stanols** lack a double bond in the sterol ring. Stanols, especially sitostanol and campestanol, comprise only about 10% of total dietary phytosterols (**Figure 3**).

Figure 1. Chemical Structure of Cholesterol



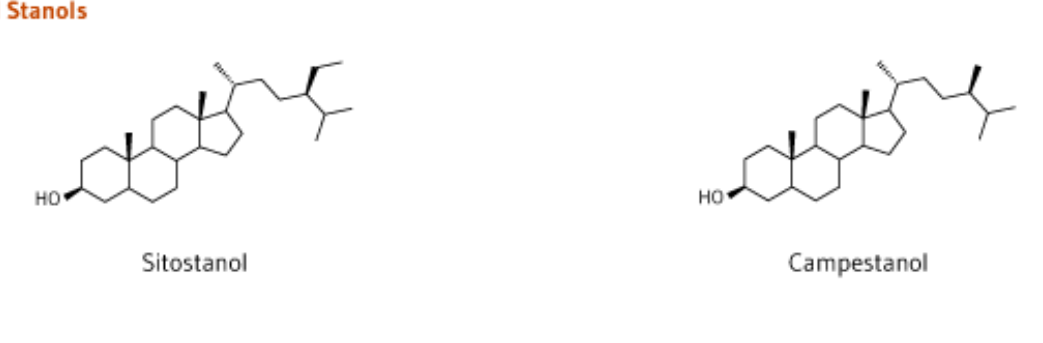
[Figure 1 - Click to Enlarge]

Figure 2. Plant-derived Sterols



[Figure 2 - Click to Enlarge]

Figure 3. Plant-derived Stanols



[Figure 3 - Click to Enlarge]

Definitions

Phytosterols: a collective term for plant-derived sterols and stanols.

Plant sterols or stanols: terms generally applied to plant-derived sterols or stanols; these phytochemicals are added to food or supplements.

Plant sterol or stanol esters: plant sterols or stanols that have been esterified by creating an ester bond between a fatty acid and the sterol or stanol. Esterification occurs in intestinal cells and is also an industrial process. Esterification makes plant sterols and stanols more fat-soluble so they are easily incorporated into fat-containing foods, including margarines and salad dressings. In this article, the weights of plant sterol and stanol esters are expressed as the equivalent weights of free (unesterified) sterols and stanols.

Metabolism and Bioavailability

Absorption and metabolism of dietary cholesterol

Dietary cholesterol must be incorporated into mixed micelles in order to be absorbed by the cells that line the intestine (enterocytes) (4). Mixed micelles are mixtures of bile salts, lipids, and sterols formed in the small intestine after a fat-containing meal is consumed. Transport across the apical membrane of enterocytes is mediated by intestinal cholesterol transporter, Niemann Pick C1-Like 1 (NPC1L1), which is also involved in the uptake of phytosterols (5). Inside the enterocyte, cholesterol is esterified in a reaction catalyzed by intestinal acyl-coenzyme A (CoA) cholesterol acyltransferases (ACATs; also present in the liver) and incorporated into triglyceride-rich lipoproteins known as chylomicrons, which are secreted into the intestinal lymphatics. The thoracic lymphatic duct then collects most of the lymph before draining into the systemic blood circulation (6). As circulating chylomicrons become depleted of triglycerides, they become chylomicron remnants, which are taken up by the liver. In the liver, cholesterol from chylomicron remnants may be repackaged into other lipoproteins for transport throughout the circulation or, alternatively, secreted into bile, which is released into the small intestine.

Absorption and metabolism of dietary phytosterols

Although varied diets typically contain similar amounts of phytosterols and cholesterol, serum phytosterol concentrations are usually several hundred times lower than serum cholesterol concentrations in humans (7). Less than 5% of dietary plant sterols and less than 0.5% of dietary plant stanols are systemically absorbed, in contrast to about 50%-60% of dietary cholesterol (8, 9). Like cholesterol, phytosterols must be incorporated into mixed micelles before they are taken up by enterocytes. Once inside the enterocyte, systemic absorption of phytosterols is inhibited by the activity of an efflux transporter, consisting of a pair of ATP-binding cassette (ABC) proteins known as ABCG5 and ABCG8. ABCG5 and ABCG8 each form one half of a transporter that secretes phytosterols and unesterified cholesterol from the enterocyte into the intestinal lumen. Phytosterols are secreted back into the intestine by ABCG5/G8 transporters at a much greater rate than cholesterol, resulting in much lower intestinal absorption of dietary phytosterols than cholesterol (10).

Within the enterocyte, phytosterols are not as readily esterified as cholesterol, so they are incorporated into chylomicrons at much lower concentrations. Those phytosterols that are incorporated into chylomicrons enter the circulation and are taken up by the liver. Once inside the liver, phytosterols are rapidly secreted into bile by hepatic ABCG5/G8 transporters. Although cholesterol is also secreted into bile, the rate of phytosterol secretion into bile is much greater than cholesterol secretion (11). Thus, the low serum concentrations of phytosterols relative to cholesterol can be explained by decreased intestinal absorption and increased excretion of phytosterols into bile.

Biological Activities

Effects on cholesterol absorption and excretion

It is well established that high intakes of plant sterols or stanols can lower serum total and low-density lipoprotein (LDL)-cholesterol concentrations in humans (see Cardiovascular disease). Different mechanisms appear to underlie the cholesterol-lowering effect of phytosterols (reviewed in 12). In the intestinal lumen, phytosterols displace cholesterol from mixed micelles and reduce cholesterol absorption (13). It is also suggested that phytosterols might interfere with the esterification and incorporation of cholesterol into chylomicrons inside the enterocytes (12). In a placebo-controlled, cross-over trial, the consumption of moderate (0.46 g/day) and high (2.1 g/day) phytosterol-enriched beverages reduced cholesterol absorption by about 10% and 25%, respectively (14). Moderate and high phytosterol intakes also significantly increased the excretion of biliary and dietary cholesterol in the feces by 36% and 74%, respectively (14). Although the mechanisms are currently not clear, phytosterols might facilitate cholesterol efflux from peripheral tissues and macrophages lining vessel walls. Cholesterol is then transported to the liver and incorporated into bile stored in the gallbladder. While plant sterols may promote the hepatobiliary secretion of cholesterol into the intestinal lumen, they are also hypothesized to facilitate the disposal of cholesterol via a nonbiliary route called transintestinal cholesterol efflux (TICE) (12).

Effects on cholesterol metabolism

A decrease in intestinal-derived cholesterol entering the circulation as chylomicrons triggers the endogenous production of cholesterol in order to maintain cholesterol homeostasis (14). Cell surface LDL-receptor expression is also up-regulated to enhance a receptor-mediated uptake of circulating LDL-cholesterol into cells (15). This process results in an increased clearance of circulating LDL from the blood. Within the cells, LDL particles are dismantled in lysosomes and cholesterol becomes available for metabolic needs. Through inhibiting the sterol regulatory element-binding protein (SREBP) pathway, LDL and LDL-derived cholesterol then suppress the transcription of the genes coding for 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase and other enzymes involved in the synthesis of cholesterol and of the LDL-receptor (16). The net result is the maintenance of cellular cholesterol homeostasis within tissues (especially in the liver) and a reduction in serum LDL-cholesterol concentration.

(especially in the liver) and a reduction in serum LDL cholesterol concentration.

Of note, some individuals with low intestinal cholesterol absorption efficiency (17) and/or high basal cholesterol synthesis rate (18) have been found to be poorly responsive to phytosterol therapy (reviewed in 19).

Other biological activities

Experiments in cell culture and animal models have suggested that phytosterols might have biological activities unrelated to cholesterol lowering. However, their significance in humans is not yet known.

Alterations in cell membrane properties

Cholesterol is an important structural component of mammalian cell membranes (20). Displacement of cholesterol with phytosterols has been found to alter the physical properties of cell membranes *in vitro* (21), which could potentially affect signal transduction or membrane-bound enzyme activity (22, 23). Limited evidence from an animal model of hemorrhagic stroke suggested that very high intakes of phytosterols could displace cholesterol in red blood cell membranes, resulting in decreased deformability and potentially increased fragility (24, 25). However, daily phytosterol supplementation (1 g/1,000 kcal) for four weeks did not alter red blood cell fragility in humans (26).

Alterations in testosterone metabolism

Limited evidence from animal studies suggests that very high phytosterol intake could alter testosterone metabolism by inhibiting 5-α-reductase, a membrane-bound enzyme that converts testosterone to dihydrotestosterone, a more potent metabolite (27, 28). It is not known whether phytosterol consumption alters testosterone metabolism in humans. No significant changes in free or total serum testosterone concentrations were observed in men who consumed 1.6 g/day of plant sterol esters for one year (29).

Anticancer effects

Phytosterols have been found to inhibit proliferation, induce apoptosis, and reduce invasiveness of cancer cells in culture (reviewed in 30). There is currently little evidence to suggest that phytosterol consumption could substantially contribute to lower the risk of cancer in humans (see Cancer).

Anti-inflammatory effects

Limited data from cell culture and animal studies suggest that phytosterols may attenuate the inflammatory activity of immune cells, including macrophages and neutrophils (31, 32). The result of a recent meta-analysis of 20 randomized controlled trials found that reductions in total cholesterol and LDL-cholesterol concentrations with phytosterol-enriched foods were not associated with changes in plasma concentration of C-reactive protein (CRP), a surrogate marker of chronic low-grade inflammation (33).

Disease Prevention

Cardiovascular disease

Typical diets across different populations have been estimated to provide 150 to 450 mg/day of naturally occurring phytosterols. Nevertheless, the consumption of vegetarian diets and of food products enriched with phytosterols can help achieve much greater intakes of phytosterols (see Food sources). Relatively few studies have considered the effects of naturally occurring dietary phytosterol intakes on serum LDL-cholesterol concentrations, while an abundance of studies have examined the lipid-lowering effect of phytosterol-enriched foods.

Foods enriched with plant sterols or stanols

Lipid-lowering effect: Elevated LDL-cholesterol concentration is a well-established risk factor in the development of atherosclerosis and coronary heart disease (34, 35). Numerous clinical trials have found that daily consumption of foods enriched with free or esterified forms of plant sterols or stanols lowers concentrations of serum total and LDL-cholesterol (36-40). This wealth of evidence has been summarized in several meta-analyses combining the results of randomized controlled trials (41-46). A dose-dependent relationship was reported between total phytosterol intake levels (from less than 1 g/day to 4 g/day) and LDL-cholesterol reduction in a recent meta-analysis of 124 human studies (47). When analyzed separately, plant sterols and stanols showed similar dose-response effects on LDL-cholesterol concentrations for average doses ranging from 0.6 g/day to 3.3 g/day. Average doses of phytosterols between 0.6 and 1.1 g/day were found to significantly lower LDL-cholesterol concentrations by at least 5%, while an average intake of 3.3 g/day resulted in reductions of about 12.4% (47).

Another meta-analysis that analyzed the results of 59 randomized controlled trials suggested that reductions in LDL-cholesterol were greater in those with higher baseline concentrations of LDL-cholesterol (41). Interestingly, a recent meta-analysis of 15 randomized controlled trials investigating the effects of phytosterol-enriched food intake (1.8 to 6 g/day of phytosterols) in patients treated with statins (drugs that inhibit endogenous cholesterol synthesis) found that co-administration of phytosterols and statins significantly reduced total cholesterol and LDL-cholesterol concentrations compared to statin therapy alone (48). The concentrations of HDL-cholesterol and triglycerides were unaffected by the combination of phytosterols and statins compared to statin alone. In subgroup analyses, the effect of combining phytosterols and statins on blood lipid profile was not found to be significantly influenced by lipid baseline values, phytosterol dosage, or study duration (48).

Effect on vascular health: Impairment of vascular endothelial function is considered to be an early step in the development of atherosclerosis and cardiovascular disease (49). A recent 12-week randomized, double-blind, placebo-controlled study in 240 subjects with hypercholesterolemia (serum cholesterol ≥5 mmol/L [≥193 mg/dL]) found no effect of consuming 3 g/day of phytosterols added to low-fat spread on brachial artery flow-mediated dilation (FMD), a surrogate marker of endothelial health (50). Assessment of arterial stiffness — using measures of aortic pulse wave velocity (PWV) and augmentation index (AI) — and blood pressure also showed no difference between supplemented and placebo groups, despite a significant 6.7% reduction in total and LDL-cholesterol. Other trials in individuals with hypercholesterolemia (51, 52) and type 1 diabetes mellitus (53) also failed to find an effect of phytosterol-enriched spread consumption on brachial artery diameter, FMD, and/or arterial stiffness. Nonetheless, the results of a randomized controlled trial in 92 individuals of whom 72% had serum cholesterol ≥5 mmol/L suggested beneficial effects of plant stanol-enriched spread consumption (corresponding to 3 g/day of stanols for six months) on arterial stiffness and endothelial function, as assessed by cardio-ankle vascular index (CAVI) and reactive hyperemia index (RHI) measures, respectively (54). Finally, a 21-month randomized controlled trial used retinal photography to examine the effect of phytosterol-enriched margarine consumption on retinal microcirculation in 43 statin-treated subjects (55). Reductions in LDL-cholesterol concentration by 9.7% and 11.2% with plant sterols (2.5 g/day) and plant stanols (2.5 g/day), respectively, were not accompanied by significant changes in the diameter of retinal arterioles and venules, a proxy measure to assess microvascular health (55). At present, whether phytosterols can improve vascular health in individuals with endothelial dysfunction is unclear. The lack of an effect of phytosterols in most of the abovementioned trials may be due to the inclusion of apparently healthy participants who may have normal endothelial function (50).

Effect on the risk of coronary heart disease: Elevated LDL-cholesterol is an established risk factor for coronary heart disease (CHD) (56). The pooled analysis of 27 randomized controlled trials of statin drug therapy found a 24% decrease in the risk of major coronary events and a 12% decrease in vascular mortality per 1 millimol/L (1 mM) reduction in LDL-cholesterol concentration, irrespective of gender and level of cardiovascular risk (57). Yet, at present, the effect of long-term use of foods enriched with plant sterols or stanols on CHD risk is not known.

The addition of plant sterol- or stanol-enriched foods to a heart-healthy diet that is low in saturated fat and rich in fruit and vegetables, whole grains, and fiber offers the potential for additive effects in CHD risk reduction. For example, following a diet that substituted monounsaturated and polyunsaturated fats for saturated fat resulted in a 9% reduction in serum LDL-cholesterol after 30 days, but the addition of 1.7 g/day of plant sterols to the same diet resulted in a 24% reduction (58). In addition, one-month adherence to a diet providing a portfolio of cholesterol-lowering foods, including plant sterols (1 g/1,000 kcal), soy protein, almonds, and viscous fibers, lowered serum LDL-cholesterol concentrations by an average of 30% — a decrease that was not significantly different from that induced by statin therapy (59).

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III included the use of plant sterol or stanol esters (2 g/day) as a component of maximal dietary therapy for elevated LDL-cholesterol (60). The 2013 report of the American College of Cardiology (ACC) task force advised clinicians to consider the use of phytosterol-enriched foods as dietary adjuncts for high-risk patients with insufficient LDL-cholesterol response to statin therapy (61). However, stepping back from a general recommendation, the ACC and American Heart Association (AHA) did not include phytosterols in their 2013 report on lifestyle management guidelines to reduce cardiovascular risk (62). Likewise, the 2015-2020 Dietary Guidelines for Americans — issued jointly by the US Department of Health and Human Services and the US Department of Agriculture — does not mention phytosterols in the composition of healthy eating patterns (63).

The US Food and Drug Administration (FDA) has authorized the use of health claims on food labels indicating that regular consumption of foods enriched with plant sterol or stanol esters, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease (see Foods enriched with plant sterols and plant stanols) (61, 64). In the EU, disease risk reduction claims for phytosterols are restricted to certain fortified food products and include a number of mandatory statements such as the fact that these products are not intended for people who do not need to control their blood cholesterol level (65).

Dietary phytosterols

Clinical trials finding daily consumption of foods enriched with plant sterols or stanols can significantly lower LDL-cholesterol concentrations do not account for naturally occurring phytosterols in the diet (66). Relatively few studies have considered the effects of dietary phytosterol intakes on serum LDL-cholesterol concentrations. Limited evidence, primarily from cross-sectional studies, suggests that dietary phytosterols may play an important role in decreasing cholesterol absorption. A cross-sectional study in the UK found that dietary phytosterol intakes were inversely related to serum total and LDL-cholesterol concentrations even after adjusting for saturated fat and fiber intake (67). Similarly, an analysis in a Swedish population found that dietary intake of phytosterols was inversely associated with total cholesterol in both men and women and with LDL-cholesterol in women (68). Dietary phytosterol intakes were also found to be inversely associated with LDL-cholesterol concentrations in another cross-sectional study in healthy Spanish participants (69). In single-meal tests, removal of 150 mg of phytosterols from corn oil increased cholesterol absorption by 38% (70), and removal of 328 mg of phytosterols from wheat germ increased cholesterol absorption by 43% (71). Although these findings suggest that moderate intakes of phytosterols could have an important impact on cardiovascular health, the intake of phytosterols (83 to 966 mg/day) from natural sources was not found to be associated with reduced risks of CHD, myocardial infarction, or total cardiovascular disease during the 12.2-year follow-up of 35,597 participants of the European Prospective Investigation into Cancer and Nutrition-The Netherlands (EPIC-NL) (72).

Cancer

Limited data from animal studies suggest that very high intakes of phytosterols, particularly sitosterol, may inhibit the growth of breast and prostate cancer (reviewed in 73). Only a few observational studies have examined associations between dietary phytosterol intakes and cancer risk in humans (30). A series of case-control studies in Uruguay found that dietary phytosterol intakes were lower in people diagnosed with stomach, lung, or breast cancer than in cancer-free control groups (74-76). Case-control studies in the US found that women diagnosed with breast or endometrial (uterine) cancer had lower dietary phytosterol intakes than women who did not have cancer (77, 78). In contrast, another case-control study in the US found that men diagnosed with prostate cancer had higher dietary campesterol intakes than cancer-free men, but total phytosterol consumption was not associated with prostate cancer risk (79). Although higher intakes of plant foods containing phytosterols may be associated with lower cancer risk, it is not clear whether potential anticancer health benefits can be attributed to phytosterols or to other compounds in plant foods (e.g., other phytochemicals, vitamins, minerals, and fiber).

Disease Treatment

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is the term used to describe a noncancerous enlargement of the prostate. The enlarged prostate may exert pressure on the urethra, resulting in difficulty urinating. Plant extracts that provide a mixture of phytosterols (marketed as β-sitosterol) are often included in herbal therapies for urinary symptoms related to BPH. However, relatively few controlled studies have examined the efficacy of phytosterol supplements in men with symptomatic BPH. In a six-month study of 200 men with symptomatic BPH, 60 mg/day of a β-sitosterol preparation improved symptom scores, increased peak urinary flow, and decreased post-void residual urine volume compared to placebo (80). A follow-up study reported that these improvements were maintained for up to 18 months in the 38 participants who continued β-sitosterol treatment (81). Similarly, in a six-month study of 177 men with symptomatic BPH, 130 mg/day of a different β-sitosterol preparation improved urinary symptom scores, increased peak urinary flow, and decreased post-void residual urine volume compared to placebo (82). A systematic review that combined the results of these and two other controlled clinical trials found that β-sitosterol extracts increased peak urinary flow by an average of 3.9 mL/second and decreased post-void residual volume by an average of 29 mL (83). Although the results of a few clinical trials suggest that relatively low doses of phytosterols can improve lower urinary tract symptoms related to BPH, further research is needed to confirm these findings (84).

Sources

Food

Unlike the typical diet in most developed countries today, the diets of our ancestors were rich in phytosterols, likely providing as much as 1 g/day (1). Present-day dietary phytosterol intakes have been estimated to vary from 150 to 450 mg/day in different populations (85). Vegetarians, particularly vegans, generally have the highest intakes of dietary phytosterols (86). Phytosterols are found in all plant foods, but the highest concentrations are found in unrefined plant oils, including vegetable, nut, and olive oils (3). Nuts, seeds, whole grains, and legumes are also good dietary sources of phytosterols (4). The phytosterol content of selected foods are presented in **Table 1**. For information on the nutrient content of specific foods, search the USDA food composition database.

Table 1. Total Phytosterol Content of Selected Foods

Food	Serving	Phytosterols* (mg)
Soybeans, mature seeds, raw	½ cup	149
Peas, green, mature seeds, raw	½ cup	133
Sesame oil	1 tablespoon (14 g)	118
Kidney beans, mature seeds, raw	½ cup	117
Pistachio nuts	1 ounce (49 kernels)	61
Safflower oil	1 tablespoon (14 g)	60
Lentils, pink or red, mature seeds, raw	½ cup	54
Cashew nuts	1 ounce	45
Soybeans, green, cooked, boiled	½ cup	45
Cottonseed oil	1 tablespoon (14 g)	44
Orange, raw	1 fruit	34
Macadamia nuts	1 ounce (10-12 kernels)	33
Almonds, blanched	1 ounce	32
Olive oil	1 tablespoon (14 g)	30
Banana, raw	1 large	24
Brussels sprouts, raw	1 cup	21

*In the USDA food composition database, the values of phytosterol content of foods are likely to be underestimates since they account only for major sterols (sitosterol, campesterol, and stigmasterol). In addition, the values correspond to the amounts of free and esterified phytosterols in foods, because phytosterol glycosides are not quantified by the current method unless glycosides (sugars) are removed before quantification (87).

Food enriched with plant sterols and plant stanols

Clinical trials that demonstrated a cholesterol-lowering effect have primarily used plant sterol or stanol esters solubilized in fat-containing foods, such as margarine or mayonnaise (44). Additional studies indicate that low-fat or even nonfat foods can effectively deliver plant sterols or stanols if they are adequately solubilized (37, 66). Plant sterols or stanols added to low-fat yogurt (88-91), low-fat milk (92-94), low-fat cheese (95), dark chocolate (96), and orange juice (97, 98) have been reported to lower LDL-cholesterol in randomized controlled trials. A variety of foods containing added plant sterols or stanols, including margarines, mayonnaises, vegetable oils, salad dressings, yogurt, milk, soy milk, orange juice, snack bars, and meats, are available in the US, Europe, Asia, Australia, and New Zealand (37). A 2008 meta-analysis found that phytosterols added to fat spreads, mayonnaise, salad dressings, milk, or yogurt more effectively reduced LDL-cholesterol concentrations compared to phytosterols incorporated into chocolate, orange juice, cheese, meats, and cereal bars (41). In most clinical trials, dividing the daily dose of phytosterols among two or three meals appeared to effectively lower LDL-cholesterol (41). Nevertheless, consumption of the daily dose of plant sterols or stanols with a single meal has also been found to lower LDL-cholesterol in a few clinical trials (89-91, 99, 100).

In the US, FDA-authorized health claims on food labels specify that the daily dietary intake of plant sterol (≥1.3 g/day) or stanol esters (≥3.4 g/day) that has been associated with a reduced risk of heart disease should be consumed in two servings eaten at different times of the day with other foods, as part of a diet low in saturated fat and cholesterol (61, 64). In the EU, food labels must indicate that the beneficial effect of phytosterols is obtained with a daily intake of 1.5 to 3 g of plant sterols/stanols in order to use the following European Food Safety Authority (EFSA)-approved statement: "Plant sterol and stanol esters have been shown to lower blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease" (65).

Supplements

Available without a prescription in the US, β-sitosterol supplements typically contain a mixture of β-sitosterol with other phytosterols and/or with substances like pumpkin seed oil and saw palmetto extract (101). Doses of 60 to 130 mg/day of β-sitosterol have been found to alleviate the symptoms of benign prostatic hyperplasia in a few clinical trials (see Benign prostatic hyperplasia). Phytosterol and phytostanol supplements should be taken with a meal that contains fat.

Safety

In the US, plant sterols and stanols added to a variety of food products are generally recognized as safe (GRAS) by the FDA (102). Additionally, the Scientific Committee on Foods of the EU concluded that plant sterols and stanols added to various food products are safe for human use (103). However, the Committee recommended that intakes of plant sterols and stanols from food products should not exceed 3 g/day because there is no evidence of health benefits at higher intakes and there might be undesirable effects at high intakes (65).

Adverse effects

Few adverse effects have been associated with regular consumption of plant sterols or stanols for up to one year. People who consumed a plant sterol-enriched spread providing 1.6 g/day did not report any more adverse effects than those consuming a control spread for up to one year (29), and people consuming a plant stanol-enriched spread providing 1.8 to 2.6 g/day for one year did not report any adverse effects (104). Consumption of up to 8.6 g/day of phytosterols in margarine for three to four weeks was well tolerated by healthy men and women and did not adversely affect intestinal bacteria or female hormone levels (105). Although phytosterols are usually well tolerated, nausea, indigestion, diarrhea, and constipation have occasionally been reported (106).

Sitosterolemia

Sitosterolemia, also known as phytosterolemia, is a very rare hereditary disease that results from inheriting a mutation in both copies of the *ABCG5* or *ABCG8* gene (107). Individuals who are homozygous for a mutation in either transporter protein have dramatically elevated serum phytosterol concentrations due to increased intestinal absorption and decreased biliary excretion of phytosterols. Although serum cholesterol concentrations may be normal or only mildly elevated, individuals with sitosterolemia are at high risk for premature atherosclerosis. Other clinical symptoms include tuberous and tendon xanthomas (i.e., cutaneous lipid depositions), hematological abnormalities, and sometimes joint pain and arthritis.

People with sitosterolemia should avoid foods or supplements with added plant sterols (37). Two studies have examined the effect of plant sterol consumption in heterozygous carriers of sitosterolemia, a more common condition. Consumption of 3 g/day of plant sterols for four weeks by two heterozygous carriers (108) and consumption of 2.2 g/day of plant sterols for 6 to 12 weeks by 12 heterozygous carriers did not result in abnormally elevated serum phytosterols (109). Because atherosclerosis has been reported in subjects with sitosterolemia, phytosterols have been attributed atherogenic effects. However, no relationship between serum concentrations of sitosterol and campesterol and risk of cardiovascular disease has been identified in a recent meta-analysis of 17 observational studies in 11,182 participants (110).

Pregnancy and lactation

Phytosterol-enriched foods and supplements are not recommended for pregnant or breast-feeding women because their safety has not been studied (106). At present, there is no evidence that high dietary intakes of naturally occurring phytosterols, such as those consumed by vegetarian women, adversely affects pregnancy or lactation.

Drug interactions

Statins

There is some evidence showing that statin administration initially reduces plant sterol concentrations in blood. This might be attributed to the reduction of circulating LDL, the major transport lipoprotein of plant sterols, due to enhanced hepatic uptake of LDL. However, statin therapy appears to increase the absorption of plant sterols that can be then transported by the remaining LDL particles (111). Further, the LDL-cholesterol-lowering effect of plant sterols or stanols may be additive to that of statins. The result of a recent meta-analysis of controlled clinical trials suggested that consumption of 2 to 3 g/day of plant sterols or stanols by individuals on statin therapy may lower both total cholesterol and LDL-cholesterol by an additional 0.30 mmol/L (11.6 mg/dL), compared to statin alone (48).

Ezetimibe

Ezetimibe (marketed as Zetia) is another cholesterol-lowering drug that may interfere with the intestinal absorption of phytosterols, thus significantly reducing phytosterol concentration in blood (112).

Nutrient interactions

Fat-soluble vitamins (vitamins A, D, E, and K)

Because plant sterols and stanols decrease cholesterol absorption and serum LDL-cholesterol concentrations, their effects on fat-soluble vitamin status have also been studied in clinical trials. Plasma vitamin A (retinol) concentrations were not affected by consumption of plant sterol esters or plant stanol esters for up to one year (29, 44). Although the majority of studies found no changes in plasma vitamin D (25-hydroxyvitamin D_3) concentrations, one placebo-controlled study in individuals consuming 1.6 g/day of sterol esters for one year observed a small (7%) but statistically significant decrease in plasma 25-hydroxyvitamin D_3 concentrations (29). There is little evidence that plant sterol or stanol consumption adversely affects vitamin K status. Consumption of 1.6 g/day of sterol esters for six months was associated with a nonsignificant, 14% decrease in plasma vitamin K_1 (phylloquinone) concentrations, and the level of carboxylated osteocalcin, a functional indicator of vitamin K status, was unchanged (29). Other studies of shorter duration also found no change in plasma concentrations of phylloquinone (113, 114) or vitamin K-dependent clotting factors with the consumption of plant sterol and stanol esters (115). Consumption of phytosterol-enriched foods has been found to decrease plasma vitamin E (α-tocopherol) concentration in a number of studies (44, 114). However, those decreases generally do not persist when plasma α-tocopherol concentrations are standardized to LDL-cholesterol concentrations, suggesting that observed reductions in plasma α-tocopherol are due in part to reductions in its lipoprotein carrier, LDL.

A recent meta-analysis of intervention studies found no adverse effects of phytosterol-enriched food consumption (average dose of 2.5 g/day) on fat-soluble vitamin status in well-nourished people (116).

Carotenoids

Dietary carotenoids are fat-soluble phytochemicals that circulate in lipoproteins. A recent meta-analysis of randomized controlled studies reported about 5 to 20% reductions in plasma hydrocarbon carotenoids after consumption of plant sterol- or stanol-enriched foods for one month to one year (116). Even when standardized to serum total cholesterol concentrations, decreases in α-carotene, β-carotene, and lycopene may persist, suggesting that phytosterols could inhibit the absorption of these carotenoids. Total cholesterol-standardized concentrations of xanthophyll carotenoids, zeaxanthin and β-cryptoxanthin, but not lutein, were also found to be significantly reduced by 5 to 15% with the consumption of phytosterol-enriched foods (116).

Although it is not clear whether reductions in plasma carotenoid concentrations confer any health risks (see the article on Carotenoids), a few studies showed that increasing intakes of carotenoid-rich fruit and vegetables would prevent phytosterol-induced decreases in plasma concentrations of carotenoids (117). In one randomized controlled study, advice to consume five daily servings of fruit and vegetables, including one serving of carotenoid-rich vegetables, was enough to maintain plasma carotenoid levels in people consuming 2.5 g/day of plant sterol or stanol esters (118).

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Resveratrol

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日本語

Summary

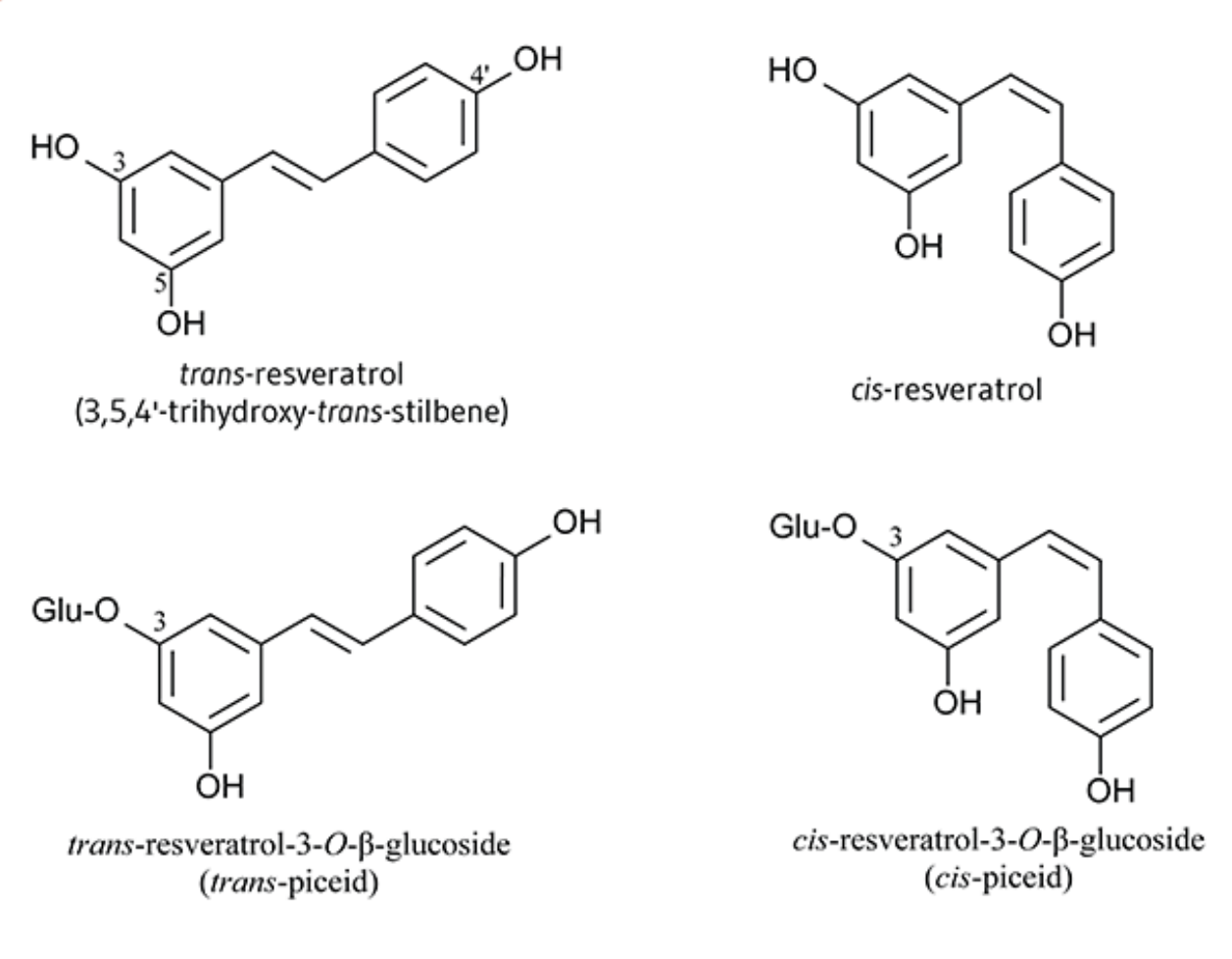
- Resveratrol is a polyphenolic compound naturally found in peanuts, grapes, red wine, and some berries. *(More information)*
- When taken orally, resveratrol is well absorbed by humans, but its bioavailability is relatively low because it is rapidly metabolized and eliminated. *(More information)*
- In preclinical studies, resveratrol has been shown to possess numerous biological activities, which could possibly be applied to the prevention and/or treatment of cancer, cardiovascular disease, and neurodegenerative diseases. *(More information)*
- Although resveratrol can inhibit the growth of cancer cells in culture and in some animal models, it is not known whether resveratrol can prevent and/or help treat cancer in humans. *(More information)*
- The presence of resveratrol in red wine was initially thought to be responsible for red wine's beneficial cardiovascular effects. Two randomized, placebo-controlled trials reported that one-year consumption of a grape supplement containing 8 mg/day of resveratrol improved inflammatory and atherogenic status in subjects at risk for cardiovascular disease, as well as in patients with established coronary heart disease. Yet, there is currently no evidence that the content of resveratrol in red wine confers any additional risk reduction beyond that attributed to the alcohol content and to other wine polyphenols. *(More information)*
- Resveratrol administration has increased the lifespans of yeast, worms, fruit flies, fish, and mice fed a high-calorie diet, but it is not known whether resveratrol will have similar effects in humans. *(More information)*
- Experimental animal studies have suggested that resveratrol might be neuroprotective and be beneficial in the prevention and/or treatment of neurodegenerative diseases; however, clinical trials in healthy or cognitively impaired older people are currently very limited. *(More information)*
- In randomized controlled trials, short-term supplementation with resveratrol significantly improved glucose and lipid metabolic disorders in patients with type 2 diabetes. *(More information)*
- Long-term, high resveratrol intake might affect the pharmacokinetics of certain drugs (i.e., those metabolized by cytochrome P450 enzymes), potentially reducing their efficacy or increasing their toxicity. *(More information)*

Introduction

Resveratrol (3,4',5-trihydroxystilbene) belongs to a class of polyphenolic compounds called stilbenes (1). Certain plants produce resveratrol and other stilbenoids in response to stress, injury, fungal infection, or ultraviolet (UV) radiation (2). Resveratrol is a fat-soluble compound that occurs in both *trans* and *cis* molecular configurations (**Figure 1**). Both *cis*- and *trans*-resveratrol also occur as glucosides, i.e., bound to a glucose molecule. One major resveratrol derivative is resveratrol-3-O-β-glucoside, also called piceid (**Figure 1**) (3).

Since the early 1990s, when the presence of resveratrol in red wine was established (4), the scientific community has been exploring the effects of resveratrol on health. Specifically, it was postulated that resveratrol intake via moderate red wine consumption might help explain the fact that French people have a relatively low incidence of coronary heart disease (CHD) in spite of consuming foods high in saturated fat, a phenomenon dubbed the "French Paradox" (see Cardiovascular disease) (5). Since then, reports on the potential for resveratrol to prevent cancer, delay the development of cardiovascular and neurodegenerative diseases, improve glycemic control in type 2 diabetes, and extend lifespan in experimental models have continued to generate scientific interest (see Disease Prevention).

Figure 1. Chemical Structures of Resveratrol and Resveratrol Glucoside (Piceid)


OH
4'
HO
3
5
OH
trans-resveratrol
(3,5,4'-trihydroxy-trans-stilbene)
HO
OH
OH
cis-resveratrol
OH
Glu-O
3
OH
trans-resveratrol-3-O-β-glucoside
(trans-piceid)
Glu-O
3
OH
OH
cis-resveratrol-3-O-β-glucoside
(cis-piceid)

Metabolism and Bioavailability

Initial studies of the pharmacokinetics of *trans*-resveratrol in humans found only traces of the unmetabolized resveratrol in the plasma upon oral exposure of single *trans*-resveratrol doses of 5 to 25 mg. Indeed, *trans*-resveratrol appears to be well absorbed by humans when taken orally, but its bioavailability is relatively low due to its rapid metabolism and elimination (6). Once absorbed, resveratrol is rapidly metabolized by conjugation to glucuronic acid and/or sulfate, forming resveratrol glucuronides, sulfates, and/or sulfoglucuronides. Sulfate conjugates are the major forms of resveratrol metabolites found in plasma and urine in humans (7).

Preliminary studies found that the administration of single oral doses of 25 mg of *trans*-resveratrol to healthy volunteers resulted in peak blood concentrations of total resveratrol (i.e., *trans*-resveratrol plus its metabolites) around 60 minutes later, at about 1.8-2 µmoles/liter (µM), depending on whether resveratrol was administered in wine, vegetable juice, or grape juice (8, 9). A study in 40 healthy subjects who received single ascending doses of oral *trans*-resveratrol (i.e., 0.5 g, 1 g, 2.5 g, and 5 g) showed that plasma concentrations of unmetabolized resveratrol peaked between 0.8 and 1.5 hours after resveratrol administration at levels ranging from 0.3 µM to 2.3 µM (10). Of note, these values were markedly below those used to elicit chemopreventive effects of resveratrol in *in vitro* experiments (>5 µM). In contrast, following a single oral dose of 5 g of *trans*-resveratrol, the peak plasma concentrations of certain resveratrol conjugates were found to be about two to eight times higher than those of unmetabolized resveratrol (10). Also, compared to a single dose administration, the repeated intake of 5 g/day of *trans*-resveratrol for 29 days was found to result in significantly greater peak plasma concentrations of *trans*-resveratrol and two resveratrol glucuronide conjugates (11). Repeated doses of 1 g/day of *trans*-resveratrol (a dose less likely to cause side effects; see Safety) could yield maximum plasma concentrations of about 22 µM for resveratrol-3-O-sulfate (the most abundant sulfate conjugate in humans) and about 7-8 µM for typical monoglucuronide conjugates (12).

A few studies have examined the influence of food matrix on resveratrol absorption and/or bioavailability (reviewed in 13). One study has reported that bioavailability of *trans*-resveratrol from red wine did not differ when the wine was consumed with a meal (low- or high-fat) versus on an empty stomach (14). Yet, in another study, the absorption of supplemental resveratrol was found to be delayed, but not reduced, by the presence of food in the stomach (15). A third study found that the bioavailability of supplemental resveratrol was reduced by the amount of fat in the diet, but not by the co-administration of quercetin (another polyphenol) or alcohol (16).

Information about the bioavailability of resveratrol in humans is important because most of the experimental research conducted to date has been 'preclinical,' i.e., *in vitro*, exposing cells to resveratrol concentrations up to 100 times greater than peak plasma concentrations observed in humans, and in animal models given very high (non dietary) doses of resveratrol (13). While cells that line the digestive tract are exposed to unmetabolized resveratrol, other tissues are likely exposed to resveratrol metabolites. At present, little is known about the biological activity of resveratrol metabolites. Yet, if some tissues are capable of converting resveratrol metabolites back to resveratrol, stable resveratrol conjugates in tissues could serve as a pool in the body from which resveratrol might be regenerated (6, 12).

Biological Activities

The biological significance of resveratrol has been primarily investigated in test tubes and cultured cells, and to a lesser extent, in animal models. Of note, a recent publication by Tomé-Carneiro et al. (13) thoroughly reviewed the most relevant preclinical studies published in the most recent decades. It is important to keep in mind that many of the biological activities discussed below were observed in cells cultured in the presence of resveratrol at higher concentrations than those likely to be achieved in humans consuming resveratrol orally (see Metabolism and Bioavailability).

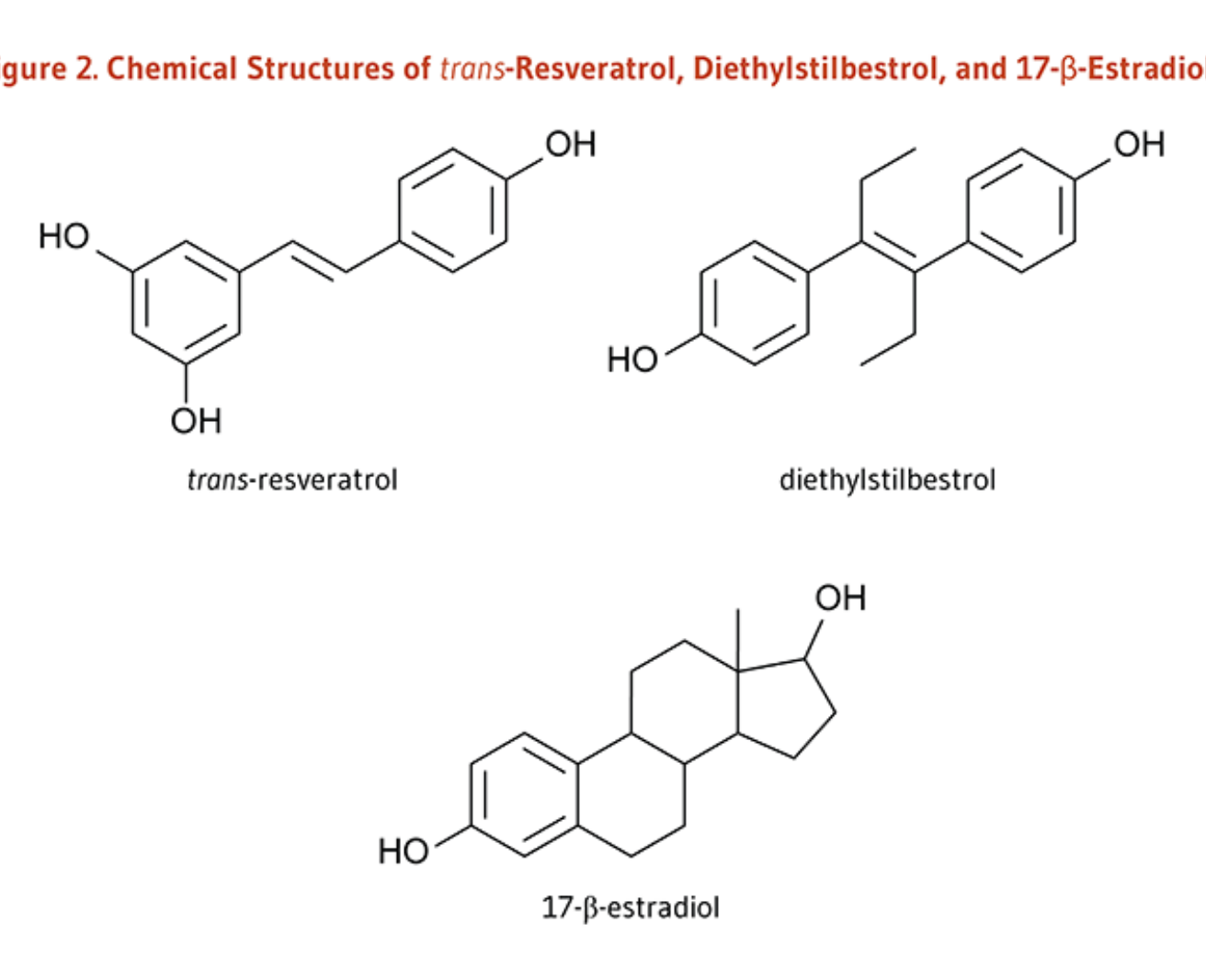
Direct antioxidant activity

In the test tube, resveratrol effectively scavenges (neutralizes) free radicals and other oxidants (17, 18) and inhibits low-density lipoprotein (LDL) oxidation (19, 20). Resveratrol was found to induce antioxidant enzymes, including superoxide dismutase (SOD), thioredoxin, glutathione peroxidase-1, heme oxygenase-1, and catalase, and/or inhibit reactive oxygen species (ROS) production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) (21). However, there is little evidence that resveratrol is an important antioxidant *in vivo*. Upon oral consumption of resveratrol, circulating and intracellular levels of resveratrol in humans are likely to be much lower than that of other important antioxidants, such as vitamin C, uric acid, vitamin E, and glutathione. Moreover, the antioxidant activity of resveratrol metabolites, which comprise most of the circulating resveratrol, may be lower than that of resveratrol (22).

Estrogenic and anti-estrogenic activities

Endogenous estrogens are steroid hormones synthesized by humans and other mammals; these hormones bind to estrogen receptors within cells. The estrogen-receptor complex interacts with unique sequences in DNA (estrogen response elements; EREs) to modulate the expression of estrogen-responsive genes (23). The chemical structure of resveratrol is very similar to that of the synthetic estrogen agonist, diethylstilbestrol (**Figure 2**), suggesting that resveratrol might also function as an estrogen agonist, i.e., might bind to estrogen receptors and elicit similar responses to endogenous estrogens. However, in cell culture experiments, resveratrol was found to act either as an estrogen agonist or as an estrogen antagonist depending on such factors as cell type, estrogen receptor isoform (ERα or ERβ), and the presence of endogenous estrogens (23). Most recently, resveratrol was shown to improve endothelial wound healing through an ERα-dependent pathway in an animal model of arterial injury (24).

Figure 2. Chemical Structures of *trans*-Resveratrol, Diethylstilbestrol, and 17-β-Estradiol



Biological activities related to cancer prevention

Effects on biotransformation enzymes

Some compounds are not carcinogenic until they have been metabolized in the body by phase I biotransformation enzymes, especially cytochrome P450 enzymes (2). By inhibiting the expression and activity of certain cytochrome P450 enzymes (25, 26), resveratrol might help prevent cancer by limiting the activation of procarcinogens. In contrast, increasing the activity of phase II detoxification enzymes generally promotes the excretion of potentially toxic or carcinogenic chemicals. Resveratrol has been found to increase the expression and activity of NAD(P)H:quinone oxidoreductase-1 (NQO1) in cultured cells (27) and may be a weak inducer of other phase II enzymes (28).

Inhibition of proliferation and induction of apoptosis

Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or activation of pathways leading to cell death (apoptosis) if the damage is irreparable (29). Defective cell cycle regulation may result in the propagation of mutations that contribute to the development of cancer. Moreover, unlike normal cells, cancer cells proliferate rapidly and are unable to respond to cell death signals that initiate apoptosis. Resveratrol has been found to induce cell cycle arrest and/or apoptosis (programmed cell death) in a number of cancer cell lines (reviewed in 13).

Inhibition of tumor invasion and angiogenesis

Cancerous cells invade normal tissue aided by enzymes called matrix metalloproteinases. Resveratrol has been found to inhibit the activity of at least one type of matrix metalloproteinase (30, 31). To fuel their rapid growth, invasive tumors must also develop new blood vessels by a process known as angiogenesis. Resveratrol has been found to inhibit angiogenesis *in vitro* (32-34) and *in vivo* (35).

Anti-inflammatory effects

Inflammation promotes cellular proliferation and angiogenesis and inhibits apoptosis (36). Resveratrol has been found to inhibit the activity of several inflammatory enzymes *in vitro*, including cyclooxygenases and lipoxygenases (37, 38). Resveratrol may also inhibit pro-inflammatory transcription factors, such as NFκB or AP-1 (39, 40).

Biological activities related to cardiovascular disease prevention

Inhibition of vascular cell adhesion molecule (VCAM) expression

Atherosclerosis is an inflammatory process in which lipids deposit in plaques (known as atheromas) within arterial walls and increase the risk of myocardial infarction (41). One of the earliest events in the development of atherosclerosis is the recruitment of inflammatory white blood cells from the blood to the arterial wall by vascular cell adhesion molecules (42). Resveratrol has been found to inhibit the expression of adhesion molecules in cultured endothelial cells (43, 44).

Inhibition of vascular smooth muscle cell (VSMC) proliferation

The proliferation of vascular smooth muscle cells (VSMCs) plays an important role in the progression of hypertension, atherosclerosis, and restenosis (when treated arteries become blocked again). Resveratrol has been found to inhibit the proliferation of VSMCs in culture (45-47), as well as *in vivo* (48). Resveratrol appeared to reduce VSMC proliferation via an ERα-dependent mechanism, hence preventing the narrowing of vessels in a mouse model of arterial injury (48).

Stimulation of endolethelial nitric oxide synthase (eNOS) activity

Endothelial nitric oxide synthase (eNOS) is an enzyme that catalyzes the formation of nitric oxide (NO) by vascular endothelial cells. NO is needed to maintain arterial relaxation (vasodilation), and impaired NO-dependent vasodilation is associated with an increased risk of cardiovascular disease (49). Because physiological concentrations of resveratrol were found to stimulate eNOS activity in cultured endothelial cells (50-52), resveratrol might help maintain or improve endothelial function *in vivo* (see Cardiovascular disease).

Inhibition of platelet activiation and aggregation

Platelet aggregation is one of the first steps in the formation of a blood clot that can occlude a coronary or cerebral artery, resulting in myocardial infarction or stroke, respectively. Resveratrol has been found to inhibit platelet activation and aggregation *in vitro* (53-55).

Biological activities related to neurodegenerative disease prevention and treatment

Stimulation of neurogenesis and microvessel formation

Age-related mood alterations and memory deficits result from a decrease in the function of the hippocampus in the elderly. Resveratrol was shown to stimulate neurogenesis and blood vessel formation in the hippocampus of healthy old rats. These structural changes were associated with significant improvements in spatial learning, memory formation, and mood function (56).

Stimulation of β-amyloid peptide clearance

One feature of Alzheimer's disease (AD) is the accumulation of β-amyloid peptide into senile (amyloid) plaques outside neurons in the hippocampus and cortex of AD patients (57). Senile plaques are toxic to cells, resulting in progressive neuronal dysfunction and death. Resveratrol was found to facilitate the clearance of β-amyloid peptide and promote cell survival in primary neurons in culture and neuronal cell lines (58-60). Resveratrol also reduced senile plaque counts in various brain regions of a transgenic AD mouse model (61).

Inhibition of neuroinflammation

Abnormally activated microglia and hypertrophic astrocytes around the senile plaques in AD brains release cytotoxic molecules, such as proinflammatory mediators and ROS, which enhance the formation and deposition of β-amyloid peptides and further damage neurons (57). Resveratrol was found able to inhibit the inflammatory response triggered by β-amyloid peptide-induced microglial activation in microglial cell lines and in a mouse model of cerebral amyloid deposition (62). A decreased occurrence of microglial activation and astrocyte hypertrophy was also reported in healthy aged rats treated with resveratrol (56).

Reduction of oxidative stress

Mitochondrial dysfunction and oxidative stress are thought to be involved in the etiology and/or progression of several neurodegenerative disorders (63). Resveratrol counteracted oxidative stress and β-amyloid peptide-induced toxicity in cultured neuroblastoma (64). Resistance against oxidative stress-related damage in primary neuronal cells treated with resveratrol has been associated with the induction of heme oxygenase-1 (HO-1), an enzyme that degrades pro-oxidant heme (65). In an experimental model of stroke, resveratrol limited infarct size during ischemia-reperfusion in wild-type mice but not in mice lacking the HO-1 gene (66). Also, resveratrol was able to correct experimentally induced oxidative stress and the associated cognitive dysfunction in rats (67).

Disease Prevention

Cancer

Resveratrol has been found to inhibit the proliferation of a variety of human cancer cell lines, including those from breast, prostate, stomach, colon, pancreatic, and thyroid cancers (2). In animal models, oral administration, topical application, and/or injection of resveratrol inhibited the development of chemically-induced cancer at many sites, including gastrointestinal tract, liver, skin, breast, prostate, and lung (reviewed in 68, 69). The anti-cancer effects of resveratrol in rodent models involved the reduction of cell proliferation, the induction of apoptosis, and the inhibition of angiogenesis, tumor growth, and metastasis (reviewed in 13). Yet, a few animal studies have reported a lack of an effect of oral resveratrol in inhibiting the development of lung cancer induced by carcinogens in cigarette smoke (70, 71), and the study of resveratrol administration on colon cancer has given mixed results (72-74).

At present, it is not known whether resveratrol might be beneficial in the prevention and/or the treatment of cancer in humans. The low bioavailability of resveratrol reported in human studies limits the clinical evaluation of possible systemic health effects of resveratrol in humans (see Metabolism and Bioavailability). Yet, in a pilot study, unmetabolized resveratrol and conjugates have been detected in colorectal tumor tissues from 20 cancer patients following daily oral supplementation with either 4 g or 8 g of resveratrol for 29 days. Resveratrol appeared to be well tolerated and significantly, though modestly, reduced cell proliferation compared to baseline (75). A micronized formulation of resveratrol (named SRT501), which was meant to increase resveratrol delivery to target tissues, was given for 14 days to 6 patients with colorectal cancer and liver metastasis in a small randomized, double-blind, placebo-controlled trial (76). Unmetabolized resveratrol was measurable in the liver of five out of six patients who consumed 5 g of SRT501, and SRT501 administration resulted in an increased detection of the apoptotic marker, cleaved caspase-3, in hepatic tumor tissues. Yet, in an unrandomized and unblinded trial in patients with multiple myeloma, the administration of SRT501 was associated with a number of serious adverse effects, including kidney failure, such that the trial was halted (77). Since kidney failure is a frequent complication in myeloma patients, it is unclear whether kidney failure cases should be solely attributed to the use of SRT501. Nevertheless, there is a need to find safe ways to increase resveratrol bioavailability in humans before exploring its putative benefits in clinical settings (6, 78).

Cardiovascular disease

Red wine polyphenols

Significant reductions in cardiovascular disease risk have been associated with moderate consumption of alcoholic beverages (79). The "French Paradox" — the observation that incidence of coronary heart disease was relatively low in France despite high levels of dietary saturated fat and cigarette smoking — led to the idea that regular consumption of red wine might provide additional protection from cardiovascular disease (80). Red wine contains variable and usually low concentrations of resveratrol (see Sources) and higher concentrations of flavonoids like procyanidins. These polyphenolic compounds have displayed antioxidant, anti-inflammatory, and other potentially anti-atherogenic effects in the test tube and in some animal models of atherosclerosis (81). The results of epidemiological studies addressing this question have been inconsistent. While some large prospective cohort studies found that wine drinkers were at lower risk of cardiovascular disease than beer or liquor drinkers (82-84), others found no difference (85-87). Socioeconomic and lifestyle differences between people who prefer wine and those who prefer beer or liquor may explain part of the additional benefit observed in some studies: people who prefer wine tend to have higher incomes, more education, smoke less, and eat more fruit and vegetables and less saturated fat than those who prefer other alcoholic beverages (87-92).

Although moderate alcohol consumption has been consistently associated with reductions in coronary heart disease risk, it is not yet clear whether red wine polyphenols confer any additional risk reduction. Interestingly, studies that administered alcohol-free red wine to rodents noted improvements in various parameters related to cardiovascular disease (93, 94), and a placebo-controlled human study found that heart disease patients administered red grape polyphenol extract experienced acute improvements in endothelial function (95). Whether increased consumption of polyphenols from red wine provides any additional cardiovascular benefits beyond those associated with red wine's alcohol content needs to be further examined (see the article on Alcoholic Beverages) (96).

Resveratrol and endothelial function

Endothelial dysfunction is usually associated with the presence of cardiovascular risk factors (e.g., insulin resistance, hypertension, and hypercholesterolemia) and is thought to precede the clinical manifestation of cardiovascular and metabolic disorders. Endothelial dysfunction is characterized by abnormal vasoconstriction, leukocyte adherence to vascular endothelial cells, platelet activation and aggregation, smooth muscle cell proliferation, vascular inflammation, thrombosis (clot formation), impaired coagulation, and atherosclerosis (97).

Experimental studies: Resveratrol has been found to exert a number of protective effects on the cardiovascular system *in vitro*, including inhibition of both platelet activation and aggregation (53, 98, 99), promotion of vasodilation by enhancing the production of nitric oxide (NO) (52), and control of the production of inflammatory lipid mediators (38, 100, 101). However, the concentrations of resveratrol required to produce these effects are often higher than those measured in human plasma after oral consumption of resveratrol (9). Some animal studies also suggested that high oral doses of resveratrol could decrease the risk of thrombosis and atherosclerosis (102, 103), although one study found increased atherosclerosis in animals fed resveratrol (104). Other protective effects of resveratrol *in vivo* include the reduction of cardiac hypertrophy and the lowering of blood pressure in various models, as well as the limitation of infarct size in post myocardial infarction rats (reviewed in 13).

Randomized controlled studies: In a six-month, cross-over study, 34 patients with metabolic syndrome were randomized to receive resveratrol (100 mg/day) for three months either immediately at the beginning of the study or three months later. Resveratrol supplementation resulted in improved values of flow-mediated dilation (FMD) of the brachial artery, a surrogate marker of vascular health. Yet, FMD returned to baseline values within three months after discontinuing resveratrol (105). One study limitation was that the resveratrol formulation contained additional compounds (i.e., vitamin D_3, quercetin, and rice bran phytate), which may also affect endothelial function. One randomized, placebo-controlled study in healthy overweight or obese volunteers (BMI, 25-34 kg/m^2) found that a single dose of *trans*-resveratrol (30 mg, 90 mg, or 270 mg) improved brachial FMD around 60 minutes after administration (106). In a second study, the same investigators found that FMD improvements were similar whether participants had received a single dose of resveratrol (75 mg) or a daily dose (75 mg/day of resveratrol) for six months (107).

In a few additional studies, resveratrol was shown to improve endothelial function by reducing vascular inflammation and endothelial activation. A randomized, double-blind, placebo-controlled study in 41 healthy subjects found that daily supplementation with resveratrol (400 mg), grapeseed extract (400 mg), and quercetin (100 mg), for one month significantly reduced the expression of interleukin-8 (IL-8) and cell adhesion molecules (ICAM-1 and VCAM-1) in endothelial cells, suggestive of a protective effect against endothelial dysfunction (108). The daily intake of a resveratrol-rich grape supplement was compared to resveratrol-free grape supplement in a year-long, randomized, double blind, placebo-controlled study in 75 individuals at high risk for cardiovascular disease (CVD). Administration of the resveratrol-rich supplement (resveratrol: 8 mg/day for 6 months, then 16 mg/day for another 6 months) significantly improved the profile of circulating inflammatory markers, reducing levels of C-reactive protein (CRP) and Tumor Necrosis Factor-α (TNF-α), as well as the level of thrombogenic factor, Plasminogen Activator Inhibitor-1 (PAI-1) (109). The decreased concentrations of two CVD risk markers, oxidized low-density lipoprotein (oxLDL) and apolipoprotein B (ApoB) after six months further suggested a cardioprotective effect of resveratrol (110). Supplementation of patients with stable coronary heart disease with the same regimen also improved the profile of circulating inflammatory markers and reduced the expression of proinflammatory genes in peripheral blood mononuclear cells (PBMCs) (111). The expression of microRNAs and cytokines specifically involved in atherogenic and pro-inflammatory signals were also found to be downregulated in the PBMCs of supplemented patients (112). Finally, although it is not clear whether hypertension is a cause or an effect of endothelial dysfunction, a recent meta-analysis of randomized controlled trials suggested that high doses of resveratrol (≥150 mg/for at least one month) might help lower systolic blood pressure in individuals at risk for CVD (113).

While preliminary human studies suggest that resveratrol may have beneficial effects on cardiovascular health, there is currently no convincing evidence that these effects can be achieved in the amounts present in one to two glasses of red wine (see Sources). For more information regarding resveratrol and cardiovascular disease, see (114).

Longevity

Caloric restriction is known to extend the lifespan of a number of species, including yeast, worms, flies, fish, rats, and mice (115). In yeast (*Saccharomyces cerevisiae*), caloric restriction stimulates the activity of an enzyme known as Silent information regulator 2 protein (Sir2) or sirtuin (116). Yeast Sir2 is a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase enzyme that removes the acetyl group from acetylated lysine residues in target proteins (see the article on Niacin).

Providing resveratrol to yeast increased Sir2 activity in the absence of caloric restriction and extended the replicative (but not the chronological) lifespan of yeast by 70% (117). Resveratrol feeding also extended the lifespan of worms (*Caenorhabditis elegans*) and fruit flies (*Drosophila melanogaster*) by a similar mechanism (118). Additionally, resveratrol dose-dependently increased the lifespan of a vertebrate fish (*Nothobranchius furzeri*) (119). Resveratrol was also found to extend the lifespan of mice on a high-calorie diet such that their lifespan was similar to that of mice fed a standard diet (120). Although resveratrol increased the activity of the Sir2 homologous human sirtuin 1 (SIRT1) in the test tube (117), there are no epidemiological data to link resveratrol, SIRT1 activation, and extended human lifespan. Moreover, the supraphysiological concentrations of resveratrol required to increase human SIRT1 activity were considerably higher than concentrations that have been measured in human plasma after oral consumption.

The results of a nine-year prospective cohort study in over 700 older adults (≥65 years) indicated that participants who were alive at the end of the study had baseline concentrations of total urinary resveratrol metabolites (used as a biomarker of resveratrol intake) similar to those who died during the study period (121). Based on a lack of correlation with baseline inflammatory markers, cardiovascular disease and cancer incidence, and all-cause mortality, the authors concluded that higher versus lower quartiles of urinary resveratrol metabolite concentrations did not predict risk of chronic disease or mortality. However, key experts identified several limitations regarding the quality of the research (122, 123). Specifically, the use of single measures of total urinary resveratrol metabolites at baseline has been highlighted as being unlikely to reflect lifetime consumption of wine or exposure to dietary resveratrol (122).

Cognitive decline

In a mouse model of Alzheimer's disease (AD), caloric restriction has been shown to limit the production and deposition of neurotoxic β-amyloid peptide in the brain (124). Similar to the effect of caloric restriction, resveratrol was found to improve obesity and diabetes-related metabolic deregulations via the activation of metabolic sensors, including SIRT and the AMP-activated protein kinase (AMPK) (125), as well as to promote the AMPK-dependent clearance of β-amyloid peptide in the brain of an AD mouse model (60). Resveratrol has also exhibited additional neuroprotective properties in cultured cells and animal models (see Biological Activities).

Although resveratrol bioavailability to the brain is uncertain (78), a randomized, double-blind, placebo-controlled study has reported an increase in cerebral blood flow in the prefrontal cortex of healthy young subjects (ages, 18-29 years) following a single oral dose of 500 mg of resveratrol. However, resveratrol intake did not improve performance in cognitively demanding tasks undertaken during the post-administration period (126). More recently, the co-administration of resveratrol (200 mg/day) and quercetin (320 mg/day) for 26 weeks in a double-blind, placebo-controlled study significantly improved measures of memory function and enhanced blood glucose control in 46 healthy, overweight older adults (ages, 50-80 years; BMI, 25-30 kg/m^2) (127). Additional evidence of the potential of resveratrol to mimic the metabolic benefits of caloric restriction on cognitive health may come from ongoing clinical trials in both healthy older individuals and AD patients (128).

Disease Treatment

Impaired glucose tolerance and type 2 diabetes mellitus

More than one out of three American adults has impaired glucose tolerance (also known as prediabetes), which places them at increased risk of developing type 2 diabetes (129). Impaired glucose tolerance is associated with insulin resistance in skeletal muscle — the major peripheral tissue for insulin-mediated glucose uptake — as well as defective insulin secretion by pancreatic β-cells. Muscle insulin resistance, which is thought to be the earliest stage in the development of type 2 diabetes, is characterized by excess lipid exposure, impaired insulin receptor signaling, impaired glucose uptake, mitochondrial dysfunction, reduced fatty acid oxidation, and increased expression of pro-inflammatory cytokines.

In animal studies, resveratrol has been shown to improve insulin sensitivity, glucose tolerance, and lipid profiles in obese and/or metabolically abnormal animals (reviewed in 130).

In humans, short-term supplementation with resveratrol has been associated with beneficial effects on glucose and lipid metabolism in individuals with type 2 diabetes. In a randomized, double-blind, placebo-controlled study, the effect of oral resveratrol supplementation (1,000 mg/day for 45 days) on the control of glucose metabolism was assessed in 70 subjects with type 2 diabetes (131). Comparison of changes between baseline and end-of-study measures between placebo and intervention groups showed that resveratrol significantly lowered both fasting glucose and fasting insulin concentrations and improved measures of glycemic control (HbA1c level) and insulin sensitivity (HOMA-IR). In addition, the level of HDL-cholesterol was increased while the level of LDL-cholesterol and systolic blood pressure were significantly reduced. No changes were found in measures of diastolic blood pressure, total cholesterol, triglycerides, and markers of liver function (131). Additionally, in a randomized, open-label, and controlled study, the effect of oral resveratrol (250 mg/day) on glycemic control and lipid metabolism was assessed in 62 type 2 diabetics (132). During the three-month study period, changes in biochemical and clinical parameters, including fasting glucose concentration, HbA1c level, systolic and diastolic blood pressure, total cholesterol, and LDL-cholesterol, were significantly improved with resveratrol compared to control (i.e., no resveratrol). Doses as low as 10 mg/day of resveratrol also resulted in lower insulin resistance in a four-week, randomized, placebo-controlled study in 19 male subjects with type 2 diabetes (133).

Obesity (defined as a body mass index [BMI] ≥ 30 kg/m^2) is a well-known risk factor for the development of type 2 diabetes. A few clinical studies have evaluated the effects of resveratrol on key metabolic variables in overweight or obese subjects with no overt metabolic dysfunction and found little or no metabolic benefits following resveratrol treatment (134-136). Yet, at present, there is no available evidence to suggest whether overweight or obese individuals with impaired glucose tolerance could benefit from resveratrol supplements and reduce their risk of developing type 2 diabetes (137).

Current data suggest that resveratrol could improve specific metabolic variables in individuals with type 2 diabetes (138, 139), but more research is needed to assess its effect in individuals at risk for diabetes, including obese subjects with impaired glucose tolerance.

Sources

Food sources

Resveratrol is found in grapes, wine, grape juice, peanuts, cocoa, and berries of *Vaccinium* species, including blueberries, bilberries, and cranberries (140-143). In grapes, resveratrol is found only in the skins (144). The amount of resveratrol in grape skins varies with the grape cultivar, its geographic origin, and exposure to fungal infection (145). The amount of fermentation time a wine spends in contact with grape skins is also an important determinant of its resveratrol content. Because grape skins are removed early during the production process of white and rosé wines, these wines generally contain less resveratrol than red wines (4). Therefore, because of variations between types of wine, vintages, and regions, it is very difficult to provide accurate estimates of resveratrol content in the thousands of wines from worldwide wineries. Yet, it appears that resveratrol content in wine is usually low, highly variable and unpredictable, and resveratrol is only a minor compound in the complete set of grape and wine polyphenols (13).

The predominant form of resveratrol in grapes and grape juice is *trans*-resveratrol-3-O-β-glucoside (*trans*-piceid), and wines contain significant amounts of resveratrol aglycones, thought to be the result of sugar cleavage during fermentation (3, 140). Many wines also contain significant amounts of *cis*-resveratrol (see **Figure 1** above), which may be produced during fermentation or released from viniferins (resveratrol polymers) (146). Red wine is a relatively rich source of resveratrol, but other polyphenols are present in red wine at considerably higher concentrations than resveratrol (see the article on Flavonoids) (147). Estimates of resveratrol content of some beverages and foods are listed in **Table 1** and **Table 2**. These values should be considered approximate since the resveratrol content of foods and beverages can vary considerably.

Table 1. Average *trans*-Resveratrol Content of Red Wines (148)

Variety	Lowest (mg/L)	Highest (mg/L)	Mean (mg/L)	5-oz Glass (mg)
Pinot Noir	0.2	11.9	3.6 ± 2.9	0.5
Merlot	0.3	14.3	2.8 ± 2.6	0.4
Zweigelt	0.6	4.7	1.9 ± 1.2	0.3
Shiraz	0.2	3.2	1.8 ± 0.9	0.3
Cabernet Sauvignon	-	9.3	1.7 ± 1.7	0.2
Red wines (global)	-	14.3	1.9 ± 1.7	0.3

Table 2. Total Resveratrol Content of Selected Foods (140, 142, 149)

Food	Serving	Total Resveratrol (mg)
Peanuts (raw)	1 cup (146 g)	0.01-0.26
Peanuts (boiled)	1 cup (180 g)	0.32-1.28
Peanut butter	1 cup (258 g)	0.04-0.13
Red grapes	1 cup (160 g)	0.24-1.25

Supplements

Most resveratrol supplements available in the US contain extracts of the root of *Polygonum cuspidatum*, also known as *Fallopia japonica*, Japanese knotweed, or Hu Zhang (150). Red wine extracts and grape extracts (from *Vitis vinifera*) containing resveratrol and other polyphenols are also available as dietary supplements. Resveratrol supplements may contain anywhere from less than 1 milligram (mg) to 500 mg of resveratrol per tablet or capsule, but it is not known whether there is a safe and effective dosage for chronic disease prevention in humans (also see the section on Safety).

Safety

Adverse effects

In rats, daily oral administration of *trans*-resveratrol at doses up to 700 mg/kg of body weight for 90 days resulted in no apparent adverse effects (151). Other toxicity studies conducted in animal models estimated that the no-observed-adverse-effect-level (NOAEL) for resveratrol was 200 mg/kg/days and 600 mg/kg/day in rats and dogs, respectively (152). Resveratrol is not known to be toxic or cause significant adverse effects in humans, but there have been only a few controlled clinical trials to date (reviewed in 153). A trial evaluating the safety of oral *trans*-resveratrol in 10 subjects found that a single dose of 5,000 mg resulted in no serious adverse effects (10). In a follow-up study, mild-to-moderate gastrointestinal side effects, including nausea, abdominal pain, flatulence, and diarrhea, have been reported in participants who consume more than 1,000 mg/day of resveratrol for up to 29 consecutive days (11). Mild diarrhea was also reported in six out of eight individuals who consumed 2,000 mg of resveratrol twice daily for two periods of eight days in an open-label and within subject-control study (16).

Pregnancy and lactation

The safety of resveratrol-containing supplements during pregnancy and lactation has not been established (150). Because there is no known safe amount of alcohol consumption at any stage of pregnancy (154), pregnant women should avoid consuming wine as a source of resveratrol.

Estrogen-sensitive conditions

Until more is known about the estrogenic activity of resveratrol in humans, women with a history of estrogen-sensitive cancers, such as breast, ovarian, and uterine cancers, should avoid resveratrol supplements (see Estrogenic and anti-estrogenic activities) (150).

Drug interactions

Anticoagulant and antiplatelet drugs

Resveratrol has been found to inhibit human platelet aggregation *in vitro* (53, 155). Theoretically, high intakes of resveratrol (i.e., from supplements) could increase the risk of bruising and bleeding when taken with anticoagulant drugs, such as warfarin (Coumadin) and heparin; antiplatelet drugs, such as clopidogrel (Plavix) and dipyridamole (Persantine); and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, diclofenac, naproxen, and others.

Drugs metabolized by cytochrome P450

Cytochrome P450 (CYP) enzymes are phase I biotransformation enzymes involved in the metabolism of a broad range of compounds, from endogenous molecules to therapeutic agents. The most abundant CYP isoform in the human liver and intestines is cytochrome P450 3A4 (CYP3A4), which catalyzes the metabolism of about half of all marketed drugs in the US (156). Resveratrol has been reported to inhibit CYP3A4 activity *in vitro* (157, 158) and in healthy volunteers (28). Therefore, high intakes of resveratrol (i.e., from supplements) could potentially reduce the metabolic clearance of drugs that undergo extensive first-pass metabolism by CYP3A4, hence increasing the bioavailability and risk of toxicity of these drugs. Some of the many drugs metabolized by CYP3A4 include HMG-CoA reductase inhibitors (statins), calcium channel antagonists (felodipine, nicardipine, nifedipine, nisoldipine, nitrendipine, nimodipine, and verapamil), anti-arrhythmic agents (amiodarone), HIV protease inhibitors (saquinavir), immunosuppressants (cyclosporine and tacrolimus), antihistamines (terfenadine), benzodiazepines (midazolam and triazolam), and drugs used to treat erectile dysfunction (sildenafil). Of note, a recently completed clinical trial (NCT01173640) examined the potential for single and multiple doses of resveratrol (1,000 mg) to interfere with the metabolism of midazolam in healthy volunteers, and results are soon to be published (153). Other CYP enzymes (e.g., CYP2D6 and CYP2C9) may also be inhibited by resveratrol (reviewed in 159).

Finally, resveratrol was found to be a weak inducer of the expression and activity of CYP1A2, which catalyzes the metabolism of several drugs, including acetaminophen (paracetamol) and the antidepressant drugs, clomipramine and imipramine (28, 156). This suggests that resveratrol may interfere with CYP1A2-mediated drug metabolism by increasing drug clearance, possibly lowering circulating drug concentrations below therapeutic levels.

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Soy Isoflavones

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日本語

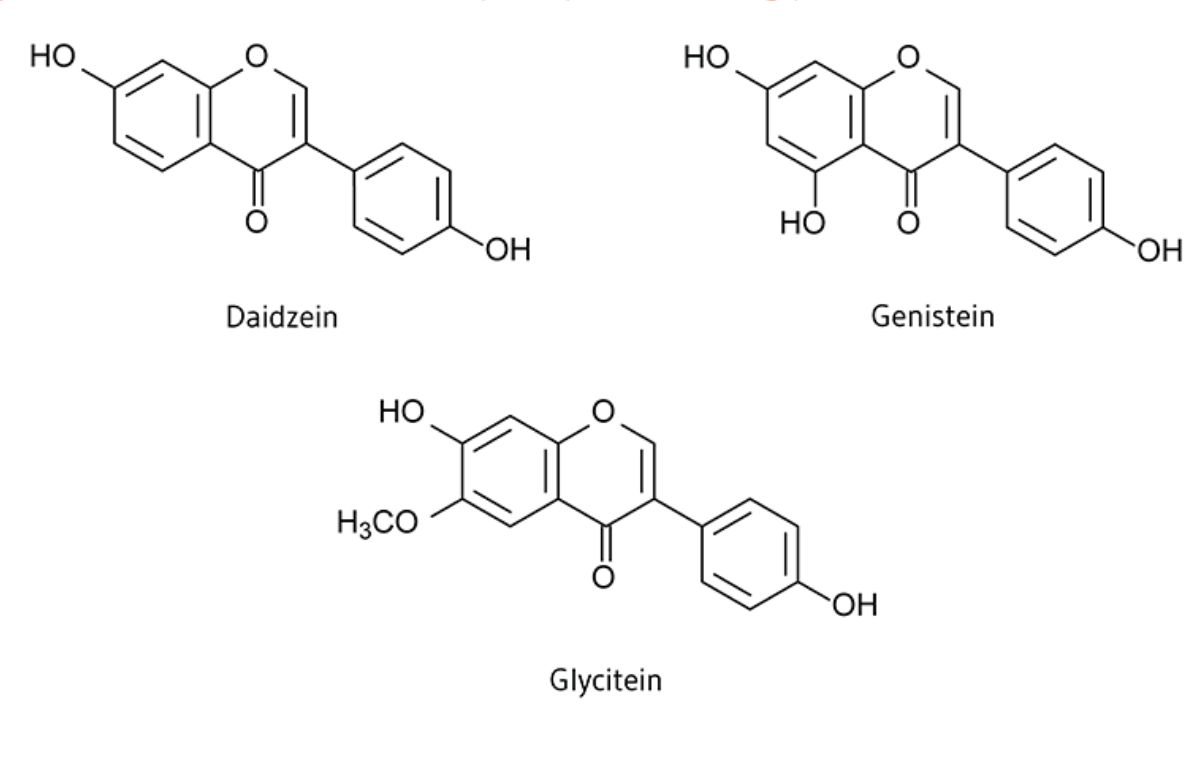
Summary

- Isoflavones are a class of phytoestrogens — plant-derived compounds with estrogenic activity. Soybeans and soy products are the richest sources of isoflavones in the human diet. *(More information)*
- Some health effects of soy may be dependent on one's capacity to convert the isoflavone daidzein to equol during digestion. *(More information)*
- The results of observational studies suggest that higher intakes of soy foods early in life may decrease the risk of breast cancer in adulthood. There is currently little clinical evidence that taking soy isoflavone supplements decreases the risk of incident and recurrent breast cancer. *(More information)*
- Current evidence from observational studies and small clinical trials is not robust enough to understand whether soy protein/isoflavone supplements may help prevent or inhibit the progression of prostate cancer. *(More information)*
- To date, randomized controlled trials examining the effect of soy isoflavones on bone mineral density in postmenopausal women have produced mixed results. Potential benefits of soy isoflavones as an alternative to bone-sparing treatments in women undergoing menopause remain to be determined. *(More information)*
- Current evidence suggests that whole soy components other than isoflavones may have favorable effects on serum lipid profiles. Yet, two recent meta-analyses of randomized controlled trials indicated that isoflavones might exert cardiovascular benefits by improving vascular function in postmenopausal women. *(More information)*
- Supplementation with isoflavones appeared to be about 40% less efficient than hormone-replacement therapy in attenuating menopausal hot flashes and required more time to reach its maximum effect. Yet, supplements containing primarily the isoflavone genistein have demonstrated consistent alleviation of menopausal hot flashes. *(More information)*
- Currently available data suggest that breast cancer survivors should not be further discouraged from consuming soy foods in moderation. Moreover, in a pooled analysis of three large prospective cohort studies, soy isoflavone intake ≥10 mg/day was associated with a 25% reduced risk of tumor recurrence in breast cancer survivors. *(More information)*
- At present, there is no convincing evidence that infants fed soy-based formula are at greater risk for adverse effects than infants fed cow's milk-based formula. *(More information)*

Introduction

Isoflavones are polyphenolic compounds that possess both estrogen-agonist and estrogen-antagonist properties (see Biological Activities). For this reason, they are classified as phytoestrogens — plant-derived compounds with estrogenic activity (1). Isoflavones are the major flavonoids found in legumes, particularly soybeans. In soybeans, isoflavones are present as glycosides, i.e., bound to a sugar molecule. Digestion or fermentation of soybeans or soy products results in the release of the sugar molecule from the isoflavone glycoside, leaving an isoflavone aglycone. Soy isoflavone glycosides include genistin, daidzin, and glycitin, while the aglycones are called genistein, daidzein, and glycitein (**Figure 1**). Unless otherwise indicated, quantities of isoflavones specified in this article refer to aglycones — not glycosides.

Figure 1. Chemical Structures of Major Soy Isoflavone Aglycones



[Click to Enlarge]

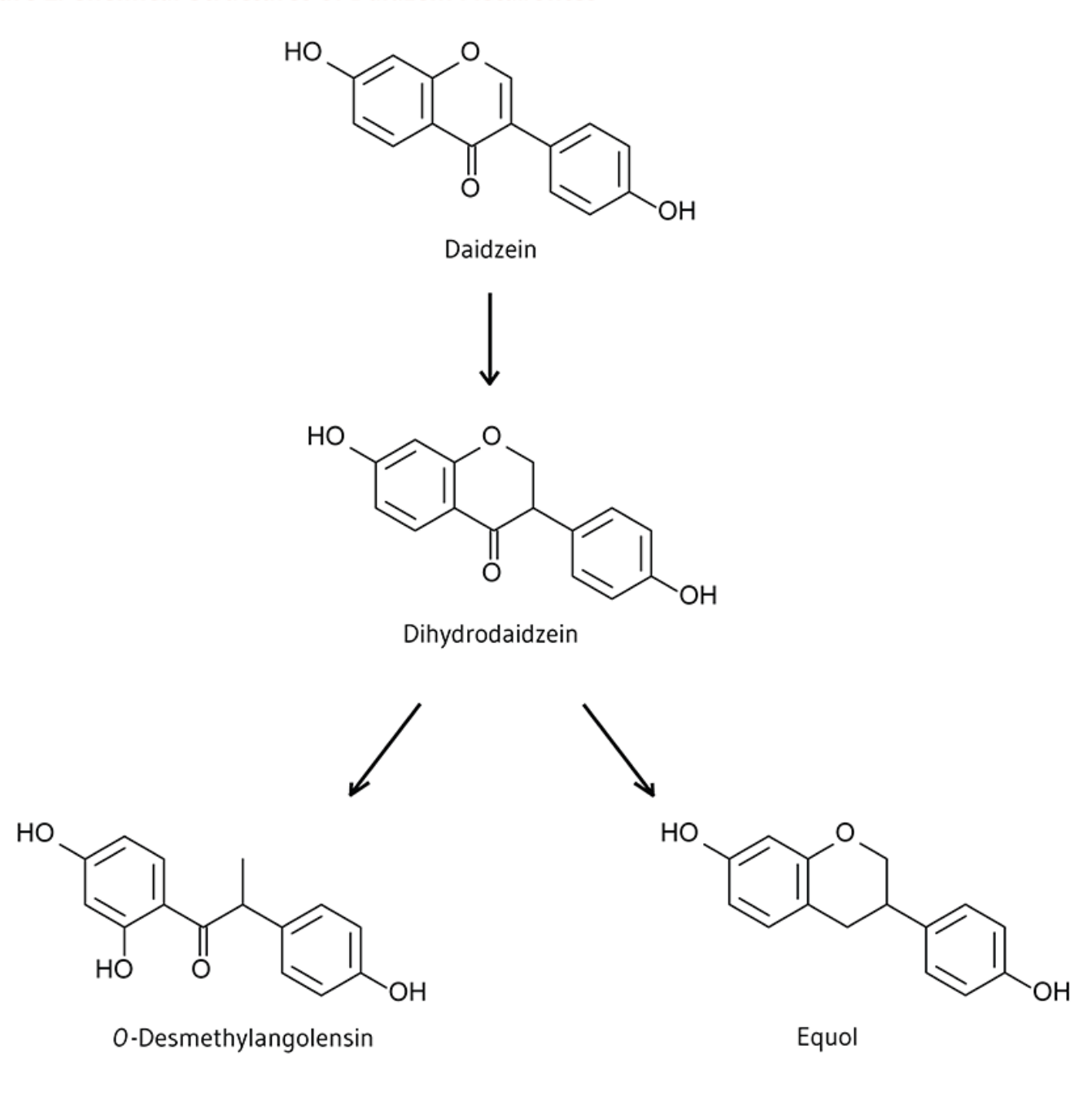
Metabolism and Bioavailability

The article on Flavonoids describes some of the factors influencing the absorption, metabolic fate, and bioavailability of flavonoid family members, including isoflavones. Pharmacokinetic studies have indicated that plasma concentrations of daidzein and genistein peaked about six hours after isoflavone intake, preceded by a smaller initial peak one hour post-meal (2, 3). The initial peak reflects isoflavone absorption following the hydrolysis of isoflavone glycosides to aglycones by β-glucosidases in the small intestine, while the second peak corresponds to isoflavone aglycones absorbed after the hydrolysis of glycosides by bacterial β-glucosidases in the colon (2).

The composition of one's colonic microbiota can influence the metabolic fate and biological effects of isoflavones. Indeed, the extent of at least some of the potential health benefits of soy intake are thought to depend on one's capacity to convert isoflavones to key metabolites during digestion. Specifically, some colonic bacteria can convert the soy isoflavone daidzein to equol, a metabolite that has greater estrogenic activity than daidzein, and to other metabolites, such as *O*-desmethylangolensin [*O*-DMA], that are less estrogenic (**Figure 2**) (4, 5). Equol appears in plasma about eight hours after isoflavone intake owing to the transit time of daidzein to the colon and its subsequent conversion to equol by the microbiota. Studies measuring urinary equol excretion after soy consumption indicated that equol was produced by about 25%-30% of the adult population in Western countries compared to 50%-60% of adults living in Asian countries and Western adult vegetarians (4, 6). Note that individuals possessing equol-producing bacteria are called "equol producers" as opposed to "equol non-producers."

Although prolonged soy food consumption has not been associated with the ability to produce equol, the type of soy food consumed might influence the composition of microbiota to include equol-producing bacteria (discussed in 4).

Figure 2. Chemical Structures of Daidzein Metabolites



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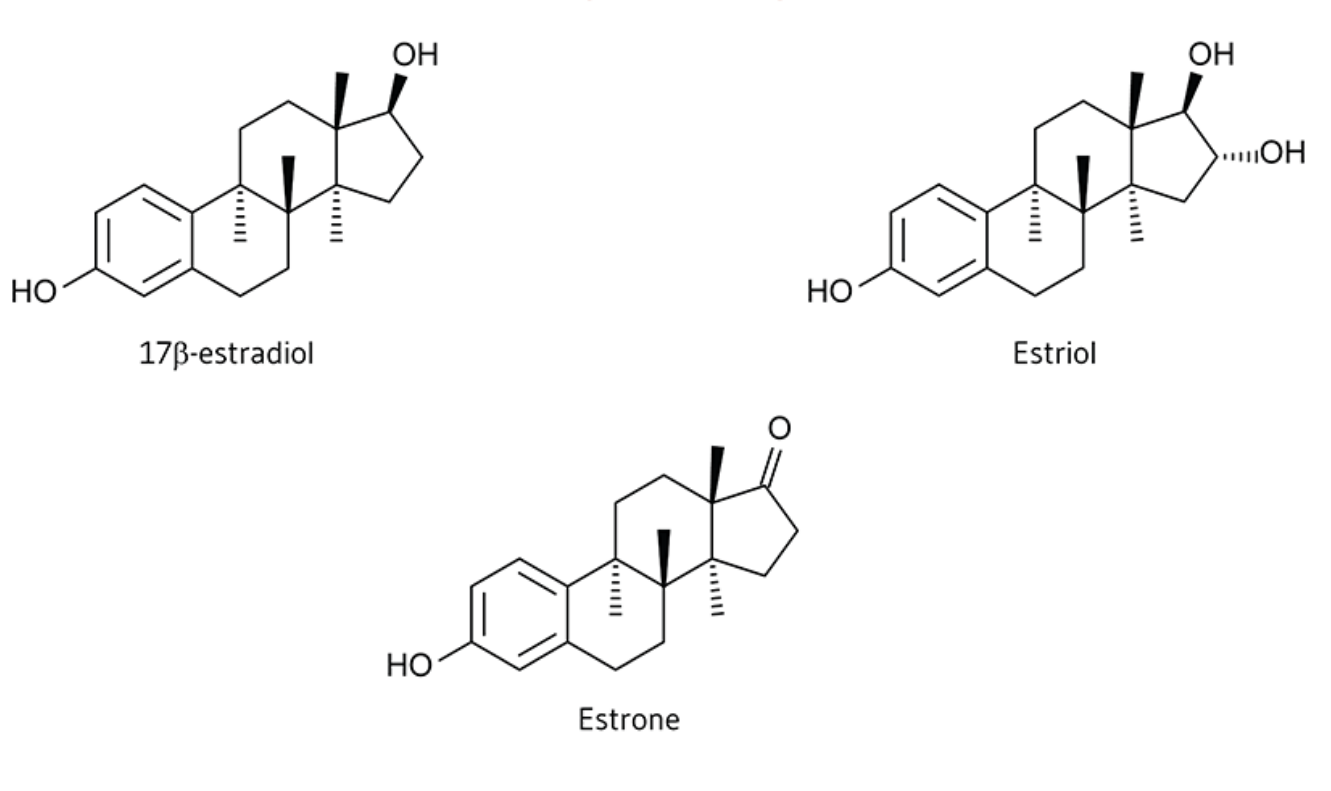
Biological Activities

Estrogenic and anti-estrogenic activities

Soy isoflavones are known to have weak estrogenic or hormone-like activity due to their structural similarity with 17-β-estradiol (**Figure 3**). Estrogens are signaling molecules that exert their effects by binding to estrogen receptors within cells (**Figure 3**). The estrogen-receptor complex interacts with DNA to change the expression of estrogen-responsive genes. Estrogen receptors (ER) are present in numerous tissues other than those associated with reproduction, including bone, liver, heart, and brain (7). Soy isoflavones can preferentially bind to and transactivate estrogen receptor-β (ER-β) — rather than ER-α — mimicking the effects of estrogen in some tissues and antagonizing (blocking) the effects of estrogen in others (8). Scientists are interested in the tissue-selective activities of phytoestrogens because anti-estrogenic effects in reproductive tissue could help reduce the risk of hormone-associated cancers (breast, uterine, and prostate), while estrogenic effects in other tissues could help maintain bone mineral density and improve blood lipid profiles (see Disease Prevention). The extent to which soy isoflavones exert estrogenic and anti-estrogenic effects in humans is currently the focus of considerable scientific research.

Figure 3. Chemical Structures of Some Endogenous Estrogens



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Estrogen receptor-independent activities

Soy isoflavones and their metabolites also have biological activities that are unrelated to their interactions with estrogen receptors (9). By inhibiting the synthesis and activity of certain enzymes involved in estrogen metabolism, soy isoflavones may alter the biological activity of endogenous estrogens and androgens (10-13). Soy isoflavones have also been found to inhibit tyrosine kinases (14), enzymes that play critical roles in the signaling pathways that stimulate cell proliferation. Additionally, isoflavones can act as antioxidants *in vitro* (15), but the extent to which they contribute to the antioxidant status of humans is not yet clear. Plasma F$_2$-isoprostanes, biomarkers of lipid peroxidation *in vivo*, were significantly lower after two weeks of daily consumption of soy protein containing 56 mg of isoflavones than after consumption of soy protein providing only 2 mg of isoflavones (16). However, daily supplementation with 50 to 100 mg of isolated soy isoflavones did not significantly alter plasma or urinary F$_2$-isoprostane concentrations (17, 18).

Disease Prevention

Hormone-associated cancers

Since soy isoflavones are structurally similar to endogenous estrogens, it has been suggested that they might help protect against hormone-associated cancers.

Breast cancer

High isoflavone intake from soy foods in Asian countries (average range, 25 to 50 mg/day) has been suggested to contribute to reducing the risk of breast cancer; in contrast, the incidence of breast cancer remains elevated in Europe, North America, and Australia/New Zealand (19) where average isoflavone intakes in non-Asian women are generally less than 2 mg/day (20). Nevertheless, several hereditary and lifestyle factors likely also contribute to this difference (19, 21). In a meta-analysis of one prospective cohort study and seven case-control studies conducted in Asian populations and in Asian Americans, higher versus lower intakes of dietary soy isoflavones (≥20 mg/day vs. ≤5 mg/day) were found to be associated with a 29% reduced risk of breast cancer (22). In observational studies conducted in Western populations, median intake of soy isoflavones was reportedly low (0.3 mg/day) and not associated with a decreased risk of breast cancer (22, 23). Moreover, a lifelong exposure to isoflavones may be needed to lower the risk of developing breast cancer later in life (21). This would explain why moderate versus low intakes of isoflavones (10.8 mg/day vs. 0.23 mg/day; cohort followed for a median of 7.4 years) during adulthood was not associated with a reduced risk of breast cancer in British women enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (24). A few case-control studies also reported that early soy exposure — during childhood and adolescence — might be associated with a lower risk of breast cancer later in life (25-28). Further, a meta-analysis of four prospective cohort studies suggested that high versus low isoflavone intakes might be associated with a modest reduction in risk of recurrence (RR=0.84, 95% CI: 0.71-0.99) in breast cancer survivors (see Safety for breast cancer survivors) (23).

While lower circulating estrogen concentrations have been linked to a lower risk of breast cancer in postmenopausal women (29), a meta-analysis of randomized controlled trials in this population found no effect of soy isoflavone supplementation on the circulating concentrations of estrogenic hormones, estradiol (21 studies) and estrone (7 studies), and of sex-hormone binding globulin (SHBG; 17 studies) (30). Another meta-analysis of seven randomized controlled trials in 1,287 women found no overall effect of soy isoflavones (40 to 120 mg/day) consumed for six months to three years on mammographic breast density, used as a surrogate marker of breast cancer risk (31). Subgroup analyses showed no effect in postmenopausal women (four studies) but a modest increase in breast density — of unclear clinical significance — in premenopausal women (five studies). Further, in a recent randomized, placebo-controlled trial, soy isoflavone supplementation (50 mg/day for one year) also failed to affect breast density in women (ages, 30 to 75 years) with breast cancer (32).

There is currently little evidence that taking soy isoflavone supplements decreases the risk of incident and recurrent breast cancer.

Endometrial cancer

It is thought that the development of endometrial (uterine) cancer could be related to prolonged exposure to unopposed estrogen, i.e., estrogen not counterbalanced with the hormone progesterone (33). Excess estrogen relative to progesterone may result in endometrial thickening, a potential biomarker of estrogen-induced proliferation and a predictor of endometrial carcinomas (34). Whether high intakes of isoflavones with anti-estrogenic activity in uterine tissue could be associated with a lower risk of endometrial cancer has been examined in a number of observational studies. A recent meta-analysis of two prospective cohort studies and eight case-control studies found the highest versus lowest quantile of isoflavone intake to be associated with a 19% lower risk of endometrial cancer (35). One of the two prospective studies included in the meta-analysis found no association between consumption of total soy foods, legumes, and tofu and risk of endometrial cancer in a cohort of 46,027 multiethnic US women (mean age at cohort entry, 61.6 years) followed for a median 13.6 years (36). Nevertheless, a 34% lower risk of endometrial cancer was found to be associated with the highest versus lowest quintile of total isoflavones (median intakes, 11.23 mg/1,000 kcal/day vs. 0.87 mg/1,000 kcal/day) in this cohort (36). In the second prospective study, no association was observed between the top versus bottom tertile of isoflavone intakes (median intakes, 63.2 mg/day vs. 17.7 mg/day) and the risk of endometrial cancer risk in 49,121 Japanese women (ages, 45 to 74 years) (37). Because the consumption of isoflavones is much lower in non-Asian versus Asian cohorts, comparisons among populations are quite problematic and limit the scope of pooled analyses of observational studies (38).

Finally, a recent meta-analysis of 23 randomized controlled trials found no overall effect of isoflavone supplementation (5 to 154 mg/day) for up to three years on endometrial thickness in postmenopausal women (39). Nevertheless, a subgroup analysis of 10 trials showed that supplementation of postmenopausal women with isoflavone doses >54 mg/day of isoflavones could significantly decrease endometrial thickness (39).

Although limited evidence from case-control studies showed an inverse relationship between consumption of soy foods and endometrial cancer, there is little evidence from intervention trials to suggest that taking soy isoflavone supplements could decrease the risk of endometrial cancer.

Prostate cancer

Incidence rates of prostate cancer are much higher in Northern America, Northern and Western Europe, Australia, and New Zealand compared to Asian countries, such as Japan and China, where isoflavone-rich soybeans are common components of the diet (19). Soy food consumption has been associated with a reduced risk of prostate cancer in recent pooled analyses of observational studies (40, 41). In a study of 19 men with prostate cancer, daily soy supplementation resulted in soy isoflavone concentrations six-fold higher in prostate tissue than in serum (42). The results of cell culture and animal studies have suggested a potential role for soy isoflavones in limiting the progression of prostate cancer (reviewed in 43).

A number of small, short-term randomized controlled interventions have examined the effect of soy foods/isoflavones on biomarkers of prostate cancer risk (44). Compared to supplementation with milk protein, consumption of a diet supplemented with soy protein isolate high in isoflavones (~107 mg/day) limited the rise in androgen receptor density in prostate tissue after six months but did not modify prostatic estrogen receptor-β expression or circulating sex steroid hormone profile in men at high risk of developing prostate cancer (45). In addition, dietary soy protein supplementation had no effect on prostate-specific antigen (PSA) in serum or markers of cell proliferation and apoptosis in premalignant tissue. Yet, supplemental soy protein isolate — regardless of isoflavone content — for six months resulted in a lower cancer incidence compared to milk control (46). In a multicenter, randomized, double-blind, placebo-controlled trial in 158 Japanese men (ages, 50 to 75 years) with negative prostate biopsy but rising serum PSA, supplemental isoflavones (60 mg/day) for one year had no effect on circulating concentrations of PSA and sex steroid hormones, or on the overall incidence of biopsy-detectable prostate cancer. However, prostate cancer incidence was found to be significantly lower with isoflavones compared to placebo in the subset of men aged 65 years and older (47).

Some trials found that supplementation with soy products, soy dietary proteins, or soy isoflavones could reduce or slow down the rising of serum PSA concentration in men with localized prostate cancer prior to therapy (48-50), as well as in those with PSA biochemical recurrence following radiotherapy and/or prostatectomy (51-53). However, other trials failed to show an effect of soy food/isoflavones on serum PSA in prostate cancer patients prior to (54, 55) or after therapy (56-58). Clinical studies have also failed to show a protective effect of soy isoflavones on circulating concentrations of sex hormones (testosterone, dihydrotestosterone, and estradiol) and sex hormone-binding globulin (SHBG) in patients with prostate cancer (44).

Pooled analyses of current data are hindered by the heterogeneity in soy/soy isoflavone preparations and dosage regimens in short-term interventions (mostly ≤6 months) in small sample-size trials. Therefore, despite a good safety profile for supplemental soy isoflavones and soy proteins in prostate cancer patients, larger randomized controlled trials with longer periods of intervention are required to assess whether soy isoflavones could influence the development and/or progression of prostate cancer.

More information about soy foods and prostate cancer risk may be found in the article on Legumes.

Osteoporosis

The decline in estrogen production that accompanies menopause places middle-aged women at risk of osteopenia and osteoporosis. The measurement of bone mineral density (BMD) loss by dual-energy X-ray absorptiometry is generally used in the diagnosis of osteoporosis (59). Whether the estrogenic properties of soy isoflavones might play any role in preserving bone health and preventing bone loss is unclear. To date, the results of observational and intervention studies examining the potential protection of soy isoflavones against BMD loss have been inconsistent. A recent review by Zheng et al. (60) discussed some potential factors relative to study design (e.g., intervention duration, isoflavone dosages) and target populations (e.g., ethnic and genetic differences, hormonal status) that could explain the conflicting study results.

For instance, the results of short-term (≤6 months) clinical trials assessing the effects of increased soy intake on biochemical markers of bone formation and bone resorption are inconsistent. Some controlled trials in postmenopausal women have found that increasing intakes of soy foods, soy protein, or soy isoflavones improved markers of bone resorption and formation (61-64) or attenuated bone loss (64, 65), but other trials have found no significant benefit of increasing soy intakes (66-69). Trials of longer duration also showed conflicting results. A meta-analysis of 10 randomized controlled trials (trial duration, 12 to 24 months) concluded that a mean dose of 87 mg/day of soy isoflavones resulted in no significant changes in lumbar spine, total hip, or femoral neck BMD of postmenopausal women (70).

Mixed results also emerged from studies conducted in different ethnic populations. Compared to Caucasian women, the incidence of hip fractures tend to be lower among Asian women who are habitual soy food consumers (71, 72), suggesting that long-term soy food consumption might protect against bone loss or osteoporotic fracture (73, 74). Moreover, pooled analyses combining intervention trials in Caucasian and Asian postmenopausal women reported significant increases in BMD with supplemental soy isoflavones (75-77). In contrast, a meta-analysis of 12 placebo-controlled trials in Caucasian postmenopausal women found no effect of soy isoflavone supplementation (dose range, 52 to 120 mg/day) for six months to three years on lumbar spine BMD (78).

The rate of bone loss is not linear during the 10-year period surrounding the final menstrual period and is especially increased during the menopausal transition, starting about one year before to two years after the final menstrual period. Surprisingly, the recent US Study of Women's Health Across the Nation (SWAN) that followed Black, White, Japanese, and Chinese women reported that Japanese women with the highest versus lowest tertile of dietary isoflavone intakes (median intakes, 36.3 mg/day versus 4 mg/day) had an increased rate of BMD loss during menopause transition (79). In other ethnic groups, no such associations could be found between habitual dietary isoflavone intakes and the rate of bone loss before, after, or during menopause transition (79). Most meta-analyses of randomized controlled trials to date have reported a weak, positive effect of supplemental soy isoflavones on BMD in postmenopausal women (70, 75-77). Yet, it remains to be elucidated whether supplementation with soy isoflavones might be of any benefit to perimenopausal/early postmenopausal women before the acute loss of estrogen or to older postmenopausal women with established osteoporosis (60).

Finally, some authors have proposed that the effect of soy isoflavones on bone health may be dependent on whether or not the individual produces the daidzein metabolite, equol (see Metabolism and Bioavailability) (80-84). However, a recent randomized controlled trial found that supplementation with soy isoflavones increased calcium retention capacity in postmenopausal women regardless of their equol-producing capacity (85).

At present, the clinical benefits of soy isoflavones as an alternative to bone-sparing treatments in women undergoing menopause remain to be determined.

Cardiovascular disease

To date, large prospective cohort studies, mainly in Asian populations, investigating whether habitual soy food/isoflavone consumption is related to the incidence of cardiovascular disease (CVD), including coronary heart disease (CHD), ischemic stroke, and myocardial infarction, have found mixed results. In the Japan Public Health Center-based Study (mean follow-up, 13.5 years), consumption of soy foods was associated with a reduced risk of stroke in Japanese women (ages, 40 to 59 years) — but not in men. In this cohort, the highest versus lowest quintile of soy isoflavone intakes was found to be associated with a 65% lower risk of ischemic stroke and a 63% lower risk of myocardial infarction in women (86). In addition, an early data analysis of 64,915 Chinese women (ages 40 to 70 years) enrolled in the Shanghai Women's Health Study (SWHS) found an inverse relationship between soy food intake and risk of incident CHD during a 2.5-year follow-up period (87). However, a higher soy protein intake was associated with a higher risk of incident CHD in 55,474 Chinese men (ages, 40 to 74 years) from the Shanghai Men's Health Study (SMHS; mean follow-up of 5.4 years) (88). Moreover, a recent report of the SWHS cohort followed for 10 years reported a 24% higher risk of ischemic stroke with the highest versus lowest quintile of isoflavone intakes (mean intakes of 59.4 mg/d versus 8.6 mg/day) (89). Nevertheless, nested case-control studies within both Shanghai prospective studies found no correlations between soy food intake and incident CVD events when measures of urinary isoflavonoids were used as a more objective estimate of isoflavone exposure compared to dietary assessment with food-frequency questionnaires (89, 90). Further, no significant associations were found between long-term soy food, soy protein, and soy isoflavone consumption and CHD-, stroke-, and total CVD-related mortality in a 14.7-year follow-up of 60,298 participants of the Singapore Chinese Health Study (91).

Low consumption of soy foods in Western cohorts makes it more difficult to analyze possible longitudinal associations between isoflavone intake and CVD incidence or mortality in these populations (92-95).

Cardiometabolic risk factors

A number of intervention studies have examined soy intake in relation to several cardiometabolic risk factors. A recent meta-analysis of randomized controlled trials concluded that intake of either soy products (i.e., whole soybeans, soy milk, nuts, oil, and flour), soy protein isolate, or soy isoflavones for one month to one year could significantly improve serum lipid profiles in healthy and hypercholesterolemic individuals by lowering circulating triglycerides, total cholesterol, and LDL-cholesterol, and by increasing HDL-cholesterol (96). Further analyses suggested that soy protein without isoflavones was more effective at lowering total and LDL-cholesterol than soy protein containing isoflavones, and the consumption of soy isoflavones alone (as supplements or extracts) showed no significant effects on serum lipid profiles (96). In addition, a meta-analysis of 18 randomized controlled studies indicated that neither soy foods nor soy isoflavones could lower blood homocysteine concentrations, a known risk factor for CVD, in high-risk middle-aged and older adults (97). Another meta-analysis of 14 randomized controlled studies reported a reduction in circulating C-reactive protein (CRP) — an inflammation marker associated with increased cardiovascular risk — following soy isoflavone intake (from soy foods or isoflavone extracts) in postmenopausal women with elevated baseline CRP concentrations (>2.2 mg/L) (98). In a recent six-month placebo-controlled intervention study in 253 postmenopausal equol-producing women with prehypertension, supplementation with whole soy — but not daidzein — improved lipid profiles and lowered the concentrations of CRP (99). Whether potential cardiovascular benefits of soy isoflavone intake depend on individuals' capacity to produce isoflavone metabolites (like equol) needs to be more closely examined.

Current evidence suggests that whole soy components other than isoflavones may have favorable effects on cardiometabolic risk factors.

Vascular function

The preservation of normal arterial function plays an important role in cardiovascular disease prevention. The ability of all types of blood vessels, including arteries, to dilate in response to nitric oxide (NO) produced by the endothelial cells that line their inner surface is compromised in people at high risk for cardiovascular disease (100). In the presence of cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, hyperglycemia), impaired endothelial function results in widespread vasodilation and coagulation abnormalities and is considered to be an early step in the development of atherosclerosis. Measures of brachial flow-mediated dilation (FMD), a surrogate marker of endothelial function, have been found to be inversely associated with risk of future cardiovascular events (101). A meta-analysis of nine small randomized, placebo-controlled trials found that supplementation with soy isoflavones (50 to 99 mg/day; isolated or from isoflavone-containing soy protein) for a median eight-week period significantly increased brachial FMD, especially in postmenopausal women with low FMD levels (102). A more inclusive meta-analysis of 17 trials in either healthy individuals or in individuals with hyperlipidemia showed an increase of FMD with the intake of isolated isoflavones but not of isoflavones-containing soy protein (103).

Arterial stiffness or impaired arterial distensibility, another marker of vascular damage and an indicator of cardiovascular disease risk, is generally assessed using measures of aortic pulse-wave velocity (PWV) (104). Some, but not all, placebo-controlled clinical trials have suggested that supplementation with isoflavone-containing soy protein or isoflavone extracts might significantly decrease arterial stiffness (105-107). A recent randomized, double-blind, placebo-controlled study found that carotid-femoral PWV could be significantly reduced 24 hours after a single oral intake of 80 mg of soy isoflavones but only in participants able to produce equol (3). Long-term interventions are needed to evaluate the clinical relevance of such a result.

Finally, whether whole soy or isoflavones reduce the burden of subclinical atherosclerosis (99, 108) and lower blood pressure (109) in individuals at high CVD risk requires further examination.

Cognitive decline

Scientific research on the effect of soy isoflavones on cognitive function has been recently reviewed by Soni et al. (110). An observational study — the Honolulu-Asia Asian Study — that examined the relationship between soy intake and cognitive function found that Hawaiian men who reported consuming tofu (non-fermented soy product) at least twice weekly during midlife were more likely to have poor cognitive test scores 20 to 25 years later than those who reported consuming tofu less than twice a week (111). In an Indonesian study of elderly men and women, consumption of tofu was associated with worse memory, while consumption of tempeh (fermented soy) was associated with improved memory (112). In the multicenter, prospective, SWAN phytoestrogen ancillary study, the highest versus lowest tertile of isoflavone intakes was found to be associated with better scores in the processing speed test but worse scores in the verbal memory test in late perimenopausal and postmenopausal Asian women (79).

The results of several randomized controlled trials have been mixed. In a review of 12 trials, only half reported an improvement in cognitive function with soy isoflavone supplementation (110). Postmenopausal women given soy extracts, providing 60 mg/day of soy isoflavones for 6 to 12 weeks, performed better on cognitive tests of picture recall (short-term memory), learning rule reversals (mental flexibility), and a planning task compared to women given a placebo (113, 114). In a longer trial, postmenopausal women given supplements that provided 110 mg/day of soy isoflavones for six months performed better on a test of verbal fluency than women given placebos (115). In a cross-over trial lasting six months, women receiving 60 mg/day of soy isoflavones experienced significant improvements in cognitive performance and overall mood compared to when the women were given a placebo (116). However, in larger placebo-controlled trials, 80 mg/day of isoflavones for six months (117) or 99 mg/day of isoflavones for one year (118) did not affect performance on a battery of cognitive function tests, including tests for memory, attention, verbal fluency, motor control, and dementia in postmenopausal women. In addition, in the 30-month Women's Isoflavone Soy Health trial in 313 postmenopausal women, daily supplementation with 91 mg of soy isoflavones significantly improved visual memory but failed to improve other aspects of cognition or global cognition (119). Nevertheless, a recent meta-analysis of 10 randomized controlled trials found a significant improvement in the pooled summary of cognitive function tests in healthy postmenopausal women supplemented with 60 to 160 mg/day of soy isoflavones for 6 to 30 months (120).

There has been little investigation regarding the potential effects of soy isoflavones in individuals with cognitive impairments (121).

Disease Treatment

Menopausal symptoms

Menopause-related vasomotor symptoms, including hot flashes (flushes) and night sweats, affect over 75% of middle-aged US women (122). Concern over potential adverse effects of hormone replacement therapy (123, 124) has led to an increased interest in the use of phytoestrogen supplements in the management of menopausal symptoms (125).

To date, the effects of increasing soy isoflavone intake on the frequency and severity of menopausal symptoms have been examined in over 60 randomized controlled trials of small sample size (126). The results of these trials have been mixed, as reflected by the conclusions of several systematic reviews and meta-analyses published in the last decade (125, 127-134). However, a systematic Cochrane review published in 2013 concluded that supplements containing primarily genistein (four studies; 30 to 60 mg/day for 12 weeks to one year) — but not dietary soy (13 studies), soy isoflavone extracts (12 studies), or red clover extracts (nine studies) — significantly reduced the frequency of hot flashes (131). This result was consistent with previous analyses reporting alleviation of hot flashes in higher- rather than lower-genistein supplementation trials (126, 133, 134). Nevertheless, in a meta-analysis by Taku et al. (133), supplemental soy isoflavone extract (30 to 80 mg/day for six weeks to one year) was found to result in a net 17.4% reduction in hot flash frequency in 13 placebo-controlled trials (1,196 women). In addition, the meta-analysis of nine trials (988 women) showed a 30.5% reduction in hot flash severity with soy isoflavone extracts (30 to 135 mg/day for 12 weeks to one year) (133). Moreover, the observation that longer trials showed a greater efficacy of soy isoflavones was confirmed in a recent model-based meta-analysis by Li et al. (135). In this analysis of 16 studies, the authors estimated that supplementation with soy isoflavones required 48 weeks of treatment, compared to only 12 weeks for estradiol, in order to achieve close to 80% of its maximum effect (135). Besides, the maximum effect of soy isoflavones was found to account for only 57% of the maximum effect of estradiol (135).

Evidence from observational studies suggested that one's ability to produce equol might contribute to reducing the occurrence or severity of menopausal symptoms in postmenopausal women (see Metabolism and Bioavailability) (136, 137). Several relatively small intervention studies have examined the potential of equol to relieve these symptoms (reviewed in 138). A recent study in Chinese postmenopausal and equol-producing women showed no benefits of daily supplementation with soy flour (40 g) or daidzein (63 mg) for six months on the frequency or severity of menopausal symptoms (139). Yet, an earlier randomized controlled study found that, compared to equol non-producing women, those able to produce equol experienced improvements in menopausal symptoms like hot flashes following soy isoflavone supplementation (135 mg/day) for six months (140). In addition, the 12-week administration of 10 mg/day of equol to equol non-producing Japanese women experiencing three or more daily hot flashes significantly reduced the frequency and severity of hot flashes and neck and shoulder muscle stiffness compared to a placebo (141). In another study, daily supplementation with soy isoflavone (containing 24 mg of daidzein and 22 mg of genistein) or equol (10, 20, or 40 mg) supplements over an eight-week period resulted in equivalent reductions of the frequency of hot flashes in postmenopausal women with five or more daily hot flashes; however, 20 mg/day and 40 mg/day of equol supplements proved to be more effective than soy isoflavone supplements in the subgroup of women experiencing eight or more hot flashes per day (142). Nevertheless, because this study lacked an inert placebo control group, the results should be viewed with caution.

At present, supplements containing sufficient amounts of genistein may help alleviate vasomotor symptoms in women transitioning through menopause (126, 143).

Sources

Food sources

Isoflavones are found in small amounts in a number of legumes, grains, and vegetables, but soybeans are by far the most concentrated source of isoflavones in the human diet (144, 145). Average dietary isoflavone intakes in Japan, China, and other Asian countries range from 25 to 50 mg/day (20). Dietary isoflavone intakes are considerably lower in Western countries. Twenty-four-hour dietary recall data collected from 36,037 individuals in 10 countries (participating in the EPIC study) showed average isoflavone intakes to be lower than 1 mg/day (146). Compared to other European countries, the isoflavone intake was slightly higher in the British general population (2.3 mg/day) and health-conscious cohort (19.4 mg/day) (146).

Traditional Asian foods made from soybeans include tofu, tempeh, miso, and natto. Edamame refers to varieties of soybeans that are harvested and eaten in their green phase. Soy products that are gaining popularity in Western countries include soy-based meat substitutes, soy milk, soy cheese, and soy yogurt. The isoflavone content of a soy protein isolate depends on the method used to isolate it. Soy protein isolates prepared by an ethanol wash process generally lose most of their associated isoflavones, while those prepared by aqueous wash processes tend to retain them (147). Some foods that are rich in soy isoflavones are listed in **Table 1**, along with their isoflavone content. Because the isoflavone content of soy foods can vary considerably among brands and among different lots of the same brand (147), these values should be viewed only as a guide. Given the potential health implications of diets rich in soy isoflavones, accurate and consistent labeling of the soy isoflavone content of soy foods is needed. Of note, foods of animal origin also contain low levels of isoflavones (and other phytoestrogens), derived from animal feeds and pastures (148). More information on the isoflavone content of foods is available from the USDA Food Composition Database website and the USDA Database for the Isoflavone Content of Selected Foods report (149).

Table 1. Total Isoflavone, Daidzein, Genistein, and Glycitein Content of Selected Foods*

Food	Serving	Total Isoflavones (mg)	Daidzein (mg)	Genistein (mg)	Glycitein (mg)
Soy protein concentrate, aqueous washed	3.5 oz	94.6	38.2	52.8	4.9
Soy protein concentrate, alcohol washed	3.5 oz	11.5	5.8	5.3	1.5
Miso	½ cup	57	22.6	32	4.1
Soybeans, mature seeds, boiled	½ cup	56	26.5	26.9	3.2
Tempeh	3 ounces	51.5	19.3	30.7	3.2
Tempeh, cooked	3 ounces	30.3	11.1	18	1.2
Soybeans, dry roasted	1 ounce	41.6	17.4	21.2	3.7
Soy milk, low-fat	1 cup	6.2	2.4	3.7	0.1
Tofu yogurt	½ cup	21.3	7.5	12.3	1.6
Tofu, soft	3 ounces	19.2	8.1	10.1	1.4
Soybeans, green, boiled (Edamame)	½ cup	16.1	6.7	6.3	4.1
Meatless (soy) burger, unprepared	1 patty	4.5	1.6	3.5	0.4
Meatless (soy) sausage	3 links	10.8	3.3	6.9	1.7
Soy cheese, cheddar	1 oz	1.9	0.5	0.6	0.8

*Isoflavone content of soy foods can vary considerably between brands and between different lots of the same brand (147); therefore, these values should be viewed only as a guide.

Supplements

Soy isoflavone extracts and supplements are available as dietary supplements without a prescription in the US. These products are not standardized, and the amounts of soy isoflavones they provide may vary considerably. Moreover, quality control may be an issue with some of these products (150). When isoflavone supplements available in the US were tested for their isoflavone content by an independent laboratory, the isoflavone content in the product differed by more than 10% from the amount claimed on the label in approximately 50% of the products tested (151).

Infant formulas

Soy protein-based infant formulas are made from soy protein isolate and contain significant amounts of soy isoflavones (**Table 2**). In 1997, the total isoflavone content of soy-based infant formulas that were commercially available in the US ranged from 32 to 47 mg/liter (~34 fluid ounces) (152).

Table 2. Total Isoflavone, Daidzein, Genistein, and Glycitein Content of Selected Soy-based Infant Formulas

Soy-based Formula	Serving	Total Isoflavones (mg)	Daidzein (mg)	Genistein (mg)	Glycitein (mg)
Mead Johnson Prosobee, ready to feed	8 fl oz.	9.4	4.1	5.3	—
Abbott Nutrition, Similac, Isomil, ready to feed	8 fl oz.	5.4	1.8	3.3	0.3
PBM products, soy, ready to feed (formerly Wyeth-Ayerst)	8 fl oz.	6.4	1.8	3.9	0.7

Safety

Soy isoflavones have been consumed by humans as part of soy-based diets for many years without any evidence of adverse effects (145). The 75th percentile of dietary isoflavone intake has been reported to be as high as 65 mg/day in some Asian populations (153). Although diets rich in soy or soy-containing products appear safe and potentially beneficial, the long-term safety of very high supplemental doses of soy isoflavones is not yet known. One study in older men and women found that 100 mg/day of soy isoflavones for six months was well tolerated (154). Yet, longer-term studies are needed to evaluate the safety of isoflavones.

Adverse effects

Safety for breast cancer survivors

The safety of high intakes of soy isoflavones and other phytoestrogens for breast cancer survivors is an area of concern among scientists and clinicians. The results of cell culture and animal studies have been conflicting; some preclinical studies showed that soy isoflavones might stimulate the growth of estrogen receptor-positive (ER+) breast cancer cells (155, 156), while others suggested that they might either potentiate (157, 158) or abrogate the anticancer effects of tamoxifen on breast tissue (159, 160).

Very limited data from clinical trials suggested that increased consumption of soy isoflavones (38 to 45 mg/day) may show weak estrogenic effects in human breast tissue (161, 162). However, a study in women with biopsy-confirmed breast cancer found that supplementation with 200 mg/day of soy isoflavones did not increase breast cell proliferation — a marker of breast cancer risk — over the two to six weeks before surgery when compared to a control group that did not take soy isoflavones (163). A few large prospective cohort studies have examined the association between soy isoflavone intake and breast cancer recurrence and survival. In the Shanghai Breast Cancer Survival Study that followed 5,042 female breast cancer survivors for a median of 3.9 years, consumption of isoflavone-rich soy foods was significantly associated with a 29% lower risk of death and a 32% lower risk of cancer recurrence (164). In this study, soy isoflavone intake was associated with a significant 23% reduced risk of cancer recurrence and a nonsignificant 21% reduced risk of death (164). A pooled analysis of data from 9,514 breast cancer survivors from the Shanghai Breast Cancer Survival Study (164), the Life After Cancer Epidemiology study (165), and the Women's Healthy Eating and Living study (166) found a 25% reduced risk of recurrence with soy isoflavone intakes ≥10 mg/day (compared to intakes of <4 mg/day) (167). A subgroup analysis showed that the inverse association between soy isoflavone intake and recurrence was significant only among women taking the anticancer drug, tamoxifen. No inverse association was reported between soy isoflavone intake and the risks of all-cause and breast cancer-specific mortality (167).

Given the available data, some experts think that women with a history of breast cancer, particularly ER+ breast cancer, should not increase their consumption of phytoestrogens, including soy isoflavones (168). Nevertheless, there is not enough evidence to discourage breast cancer survivors from consuming soy foods in moderation (143, 169).

Safety of soy protein-based infant formulas

Infant formula made from soy protein isolate has been commercially available since the mid-1960s (170). As much as 25% of the infant formula sold in the US is soy protein-based formula (171). The American Academy of Pediatrics (AAP) supports the use of soy protein isolate-based formula for normal growth and development of term infants whose needs are not being met by human milk or cow's milk-based formulas (171). Soy protein-based formulas are especially indicated for infants with galactosemia and hereditary lactase deficiency, but they have no proven value in the prevention or management of infantile colic and fussiness (171).

Since infants fed soy-based formulas are exposed to relatively high levels of isoflavones (152), which they can absorb and metabolize, concern has been raised regarding potential long-term effects on anthropometric growth, bone health, as well as reproductive, endocrine, and immune functions (152, 172). In addition to the AAP review (171), a recent systematic review and meta-analysis of data published between 1909 and 2013 found no clinical concerns regarding nutritional adequacy, sexual development, thyroid disease, immune function, and neurodevelopment in infants fed soy protein-fed formulas (173). Specifically, this review identified 14 clinical trials comparing infants fed soy-based formula with infants fed human milk or cow's milk-based formula and found that soy-based formula adequately supported growth and development in the first year of life (173). In addition, the results of three observational studies suggested no adverse effects of soy protein-based formula on the neurodevelopment of children (174-176). Two of these observational studies of low-to-moderate quality also reported associations between soy protein-based formula intake and marginal adverse events, including early menarche (176, 177) and increased duration of menstrual bleeding (176). A recent prospective cohort study (the Beginnings study) examining the effects of early infant feeding on reproductive organ development during childhood found no differences in the volume and structure of the reproductive organs of 101 five-year-old boys and girls who were either breastfed or fed soy protein- or cow's milk-based formula as infants (178). Finally, no adverse health effects have been associated with the presence of phytates and aluminum in soy protein-based formulas fed to full-term infants (reviewed in 173).

At present, there is no convincing evidence that infants fed soy protein-based formula are at greater risk for adverse effects than infants fed cow's milk-based formula. Nonetheless, if current evidence shows a safety profile for use of soy protein-based formulas in term infants, they are not designed or recommended for preterm infants (171). Also, recent preliminary findings suggesting potential links between consumption of soy protein-based formulas and adverse effects in autistic children deserve further investigation (179, 180).

Male reproductive health

Claims that soy food/isoflavone consumption can have adverse effects on male reproductive function, including feminization, erectile dysfunction, and infertility, are primarily based on animal studies and case reports (181). Exposure to isoflavones (including at levels above typical Asian dietary intakes) has not been shown to affect either the concentrations of estrogen and testosterone, or the quality of sperm and semen (181, 182). Thorough reviews of the literature found no basis for concern but emphasized the need for long-term, large scale comprehensive human studies (181, 183).

Thyroid function

In cell culture and animal studies, soy isoflavones have been found to inhibit the activity of thyroid peroxidase, an enzyme required for thyroid hormone synthesis (184, 185). However, high intakes of soy isoflavones do not appear to increase the risk of hypothyroidism as long as dietary iodine consumption is adequate (186). Since the addition of iodine to soy-based formulas in the 1960s, there have been no further reports of hypothyroidism in soy formula-fed infants (187). Several clinical trials, mostly in women with sufficient iodine intakes, have not found increased consumption of soy isoflavones to result in clinically significant changes in circulating thyroid hormone concentrations (188-192).

Pregnancy

To date, studies have not examined the effect of an isoflavone-rich diet on fetal development or pregnancy outcomes in humans, and the safety of isoflavone supplements during pregnancy has not been established.

Drug interactions

Fermented soy foods contain highly variable amounts of the biologically active amine, tyramine, which is catabolized in the body by monoamine oxidase enzyme (MAO) and excreted in the urine. The ingestion of very high amount of tyramine may saturate the detoxification system and lead to clinical symptoms of intoxication. Because individuals taking MAO inhibitors (MAOIs; phenelzine, tranylcypromine) are at greater risk of adverse effects, they should avoid consuming fermented soy products (193, 194). Because colonic bacteria play an important role in the metabolism of soy isoflavones, antibiotic therapy could decrease their biological activity (193). Some evidence from animal studies suggested that high intakes of soy isoflavones, particularly genistein, could interfere with the antitumor effects of tamoxifen (Nolvadex) (159). Yet, a recent pooled analysis of three prospective cohort studies found that the risk of recurrence in breast cancer survivors was reduced to a greater extent with soy isoflavone intake in tamoxifen users than in nonusers (see Safety for breast cancer survivors) (167). Nonetheless, until more is known about potential interactions in humans, those taking tamoxifen or other selective estrogen receptor modulators (SERMs) to treat or prevent breast cancer should be cautious and seek medical advice regarding the use of soy protein supplements or isoflavone extracts (193).

High intakes of soy protein may interfere with the efficacy of the anticoagulant medication warfarin. There is one case report of an individual on warfarin who developed subtherapeutic international normalized ratio (INR; prothrombin time) values upon consuming ~16 ounces of soy milk daily for four weeks (195). INR values returned to therapeutic levels two weeks after discontinuing soy milk.

The amount of levothyroxine required for adequate thyroid hormone replacement has been found to increase in infants with congenital hypothyroidism fed soy formula (187, 196). Taking levothyroxine at the same time as a soy protein supplement also increased the levothyroxine dose required for adequate thyroid hormone replacement in an adult with hypothyroidism (197).

Regular consumption of a diet high in soy — rather than supplementation with isoflavone extracts or isoflavone containing isolated soy protein — may help lower fasting glucose concentrations (198). It is unknown whether individuals taking antidiabetic agents might be at risk of hypoglycemia if they follow a soy-based meal replacement plan rather than a diet plan recommended by the American Diabetes Association (199).

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Chlorophyll and Metallo-Chlorophyll Derivatives

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Summary

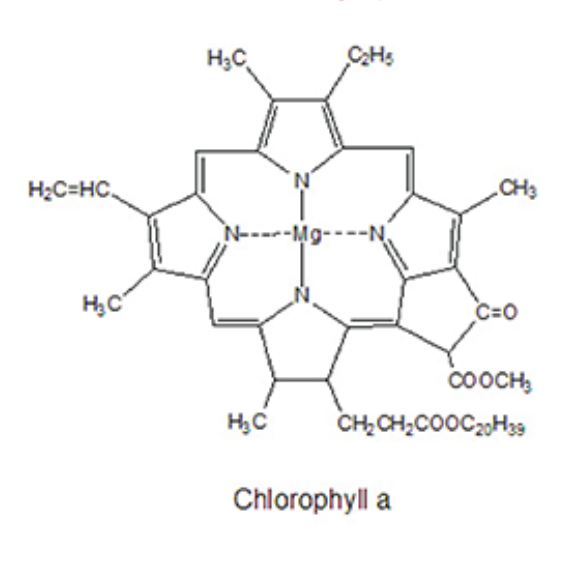
- Chlorophyll a and chlorophyll b are natural, fat-soluble chlorophylls found in plants. *(More information)*
- Sodium copper chlorophyllin (SCC) is a semi-synthetic mixture of water-soluble sodium copper salts derived from chlorophyll. *(More information)*
- SCC has been used orally as an internal deodorant and topically in the treatment of slow-healing wounds for more than 50 years without any serious side effects. *(More information)*
- Chlorophylls and SCC form tight molecular complexes with some chemicals known or suspected to cause cancer, and in doing so, may block carcinogenic effects. Carefully controlled studies have not been undertaken to determine whether a similar mechanism might limit uptake of required nutrients. *(More information)*
- Supplementation with SCC before meals substantially decreased a urinary biomarker of aflatoxin-induced DNA damage in a Chinese population at high risk of liver cancer due to unavoidable, dietary aflatoxin exposure from moldy grains and legumes. *(More information)*
- Scientists are hopeful that SCC supplementation will be helpful in decreasing the risk of liver cancer in high-risk populations with unavoidable, dietary aflatoxin exposure. However, it is not yet known whether SCC or natural chlorophylls will be useful in the prevention of cancers in people who are not exposed to significant levels of dietary aflatoxin. *(More information)*

Introduction

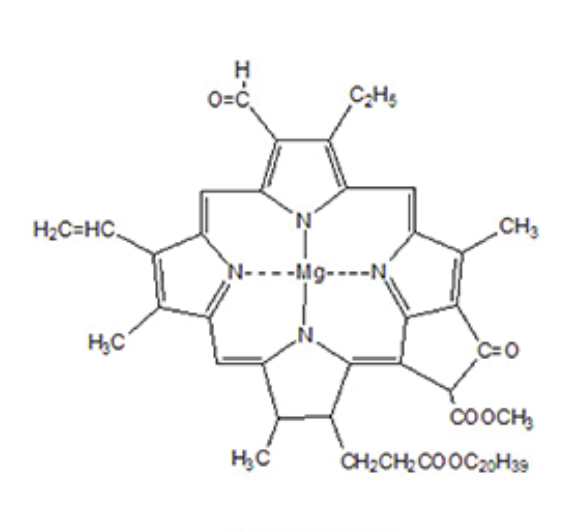
Chlorophyll is the pigment that gives plants and algae their green color. Plants use chlorophyll to trap light needed for photosynthesis (1). The basic structure of chlorophyll is a porphyrin ring similar to that of heme in hemoglobin, although the central atom in chlorophyll is magnesium instead of iron. The long hydrocarbon (phytol) tail attached to the porphyrin ring makes chlorophyll fat-soluble and insoluble in water. Chlorophyll a and chlorophyll b represent about 99% of the chlorophyll species found in edible plants (**Figure 1**; 2), while some algae and microalgae contain minor quantities of chlorophyll c pigments (e.g., *Laminaria ochroleuca*, *Undaria pinnatifida*) (3). Chlorophyll a and b only have a small difference in one of the side chains but an intact phytol tail, while the common characteristic of chlorophyll c isoforms is the absence of a phytol tail. These structural differences cause each type of chlorophyll to absorb light at slightly different wavelengths.

Metallo-chlorophyll derivatives, including chlorophyllins, can be chemically synthesized or produced in industrial food processing; these compounds contain zinc, iron, or copper in place of the central magnesium atom (2). The most studied chlorophyllin, sodium copper chlorophyllin (SCC), is a semi-synthetic mixture of sodium copper salts derived from chlorophyll (4, 5). SCC is often simply called 'chlorophyllin' in the older scientific literature, with newer publications specifying whether iron, zinc, copper, or magnesium chlorophyllin were studied. During its synthesis, the magnesium atom at the center of the ring is replaced with copper (or other metals), and the phytol tail is lost. Unlike natural chlorophyll, chlorophyllins (regardless of the metal used) are water-soluble. Although the content of different SCC mixtures may vary, two compounds commonly found in commercial SCC are trisodium copper chlorin e$_6$ and disodium copper chlorin e$_4$ (**Figure 2**).

Figure 1. Chemical Structures of Natural Chlorophylls

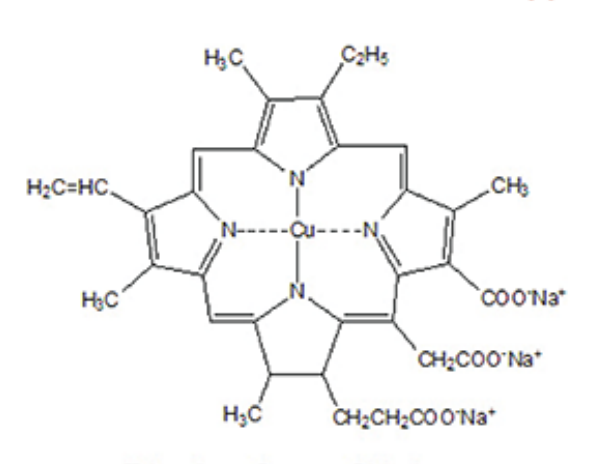


Chlorophyll a

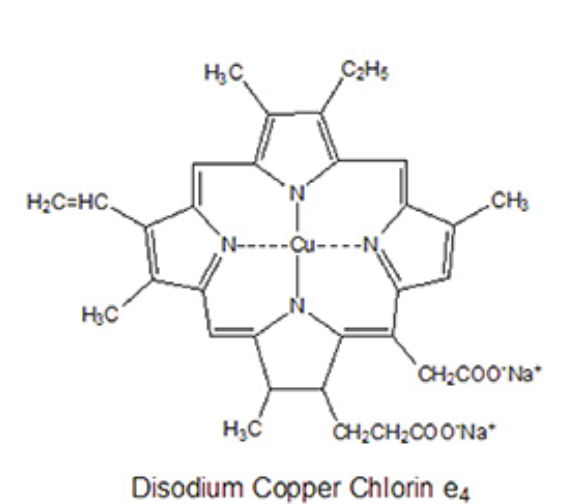


Chlorophyll b

Figure 2. Two Compounds Found in Commercial Sodium Copper Chlorophyllin



Trisodium Copper Chlorin e$_6$



Disodium Copper Chlorin e$_4$

Metabolism and Bioavailability

Little is known about the bioavailability and metabolism of chlorophyll in humans, although it is known that chlorophyll undergoes extensive metabolism once consumed. Animal model studies show only about 1%-3% of chlorophyll is absorbed, while the rest is excreted in the feces, primarily as pheopytin and pyropheophytin metabolites, indicating that significant transformation and microbial metabolism occur in the gastrointestinal tract (reviewed in 2). A recent study in eight healthy adults found pheophytin and pheophorbide derivatives in the blood of most subjects following consumption of 1.2 kg boiled spinach, a concentrated source of chlorophyll (6).

Sodium copper chlorophyllin was originally thought to be poorly absorbed because of its lack of apparent toxicity. However, a placebo-controlled clinical trial found that significant amounts of copper chlorin e$_4$ in the serum of people taking chlorophyllin tablets (300 mg/day) (7), indicating that it is indeed absorbed. *In vitro* studies have found chlorin e$_4$ to have a higher stability than chlorin e$_6$ (2).

More research, however, is needed to understand the bioavailability and metabolism of natural chlorophylls and chlorin compounds in synthetic chlorophyllin.

Biological Activities

Complex formation with other molecules

Chlorophyll and sodium copper chlorophyllin are able to form tight molecular complexes with certain chemicals known or suspected to cause cancer, including polyaromatic hydrocarbons found in tobacco smoke (8), some heterocyclic amines found in cooked meat (9), and aflatoxin-B$_1$ (10). The binding of chlorophyll or SCC to these potential carcinogens may interfere with gastrointestinal absorption of potential carcinogens, reducing the amount that reaches susceptible tissues (11). This has been demonstrated in humans: a cross-over study in three volunteers that used accelerator mass spectrometry to study the pharmacokinetics of an ultra-low dose of aflatoxin-B$_1$ found a 150-mg dose of either SCC or chlorophyll could decrease absorption of aflatoxin-B$_1$ (12).

Antioxidant effects

SCC can neutralize several physically relevant oxidants *in vitro* (13-16), and limited data from animal studies suggest that SCC supplementation may decrease oxidative damage induced by chemical carcinogens and radiation (17, 18). While chlorophyll and its derivatives have demonstrated antioxidant activity in *in vitro* assays (15, 19), the relevance of these findings to humans is not clear.

Modification of the metabolism and detoxification of carcinogens

To initiate the development of cancer, some chemicals (procarcinogens) must first be metabolized to active carcinogens that are capable of damaging DNA or other critical molecules in susceptible tissues. Since enzymes in the cytochrome P450 family are required for the activation of some procarcinogens, inhibition of cytochrome P450 enzymes may decrease the risk of some types of chemically induced cancers. *In vitro* studies indicate that SCC may decrease the activity of cytochrome P450 enzymes (8, 20, 21). Phase II biotransformation enzymes promote the elimination of potentially harmful toxins and carcinogens from the body. Limited data from animal studies indicate that SCC may increase the activity of the phase II enzyme quinone reductase (22).

Therapeutic effects

One *in vitro* study showed that human colon cancer cells undergo cell cycle arrest after treatment with SCC (23). The mechanism involved inhibition of ribonucleotide reductase activity. Ribonucleotide reductase plays a pivotal role in DNA synthesis and repair and is a target of currently used cancer therapeutic agents, such as hydroxyurea (23). While this may provide a potential avenue for SCC in the clinical setting, sensitizing cancer cells to DNA damaging agents, *in vivo* studies are needed.

Metal absorption

The porphyrin structure of chlorophyll is analogous to the heme structure found in blood and muscle tissue. Because heme-bound iron has higher bioavailability than nonheme iron (the most common form of iron in plant-based sources, e.g., legumes, spinach), iron uptake from iron chlorophyll is of interest. Toxicity studies in rats suggest iron chlorophyllin is generally safe for mammalian consumption (24). *In vitro* studies demonstrate that iron chlorophyllin is as good as heme in delivering iron to intestinal cells, and significantly better than the most common supplemental form of iron (i.e., ferrous sulfate) when incorporated into most food matrices (25). However, work in this area is nascent and has not yet been validated in humans. It is also not known if metallo-chlorophyll derivatives of copper or zinc increase absorption of these essential divalent metals.

Disease Prevention

Aflatoxin-associated liver cancer

Aflatoxin-B$_1$ (AFB$_1$), a liver carcinogen produced by certain species of fungus, is found in moldy grains and legumes, including corn, peanuts, and soybeans (4, 11). In hot, humid regions of Africa and Asia with improper grain storage facilities, high levels of dietary AFB$_1$ are associated with increased risk of hepatocellular carcinoma. Moreover, the combination of hepatitis B infection and high dietary AFB$_1$ exposure increases the risk of hepatocellular carcinoma still further. In the liver, AFB$_1$ is metabolized to a carcinogen capable of binding DNA and causing mutations. In animal models of AFB$_1$-induced liver cancer, administration of SCC at the same time as dietary AFB$_1$ exposure significantly reduces AFB$_1$-induced DNA damage in the livers of rainbow trout and rats (26-28) and dose-dependently inhibits the development of liver cancer in trout (29). Likewise, natural chlorophyll has also been found to inhibit AFB$_1$-induced liver cancer in the rat (28). Collectively, this evidence supports a role for SCC and/or chlorophyll itself in limiting cancer initiation. In contrast, data suggest a limited role for SCC in influencing cancer progression. For example, one rat study found that SCC did not protect against aflatoxin-induced liver damage when given after tumor initiation (30).

Because of the long time period between AFB$_1$ exposure and the development of cancer in humans, an intervention trial might require as long as 20 years to determine whether SCC supplementation can reduce the incidence of hepatocellular carcinoma in people exposed to high levels of dietary AFB$_1$. However, a biomarker of AFB$_1$-induced DNA damage (AFB$_1$-N^7-guanine) can be measured in the urine, and high urinary levels of AFB$_1$-N^7-guanine have been associated with significantly increased risk of developing hepatocellular carcinoma (31). In order to determine whether chlorophyllin could decrease AFB$_1$-induced DNA damage in humans, a randomized, placebo-controlled intervention trial was conducted in 180 adults residing in a region in China where the risk of hepatocellular carcinoma is very high due to unavoidable, dietary AFB$_1$ exposure and a high prevalence of chronic hepatitis B infection (32). Participants took either 100 mg of SCC or a placebo before meals three times daily. After 16 weeks of treatment, urinary levels of AFB$_1$-N^7-guanine were 55% lower in those taking SCC than in those taking the placebo, suggesting that SCC supplementation before meals can substantially decrease AFB$_1$-induced DNA damage. Although a reduction in hepatocellular carcinoma has not yet been demonstrated in humans taking SCC, scientists are hopeful that supplementation will provide some protection to high-risk populations with unavoidable, dietary AFB$_1$ exposure (11).

It is not known whether SCC will be useful in the prevention of cancers in people who are not exposed to significant levels of dietary AFB$_1$, as is the case for most people living in the US. Many questions remain to be answered regarding the exact mechanisms of cancer prevention by SCC, the implications for the prevention of other types of cancer, and the potential for natural chlorophylls in the diet to provide cancer protection.

Therapeutic Uses of Chlorophyllin

Internal deodorant

Observations in the 1940s and 1950s that topical SCC had deodorizing effects on foul-smelling wounds led clinicians to administer SCC orally to patients with colostomies and ileostomies in order to control fecal odor (33). While early case reports indicated that SCC doses of 100 to 200 mg/day were effective in reducing fecal odor in ostomy patients (34, 35), a placebo-controlled trial found that 75 mg of oral SCC three times daily was no more effective than placebo in decreasing fecal odor assessed by colostomy patients (36). Several case reports have been published indicating that oral SCC (100-300 mg/day) decreased subjective assessments of urinary and fecal odor in incontinent patients (33, 37).

Trimethylaminuria is a hereditary disorder characterized by the excretion of trimethylamine, a compound with a "fishy" or foul odor. One study in a small number of Japanese patients with trimethylaminuria found that oral SCC (60 mg three times daily) for three weeks significantly decreased urinary trimethylamine concentrations (38).

Wound healing

Research in the 1940s indicated that chlorophyllin slowed the growth of certain anaerobic bacteria in the test tube and accelerated the healing of experimental wounds in animals. These findings led to the use of topical SCC solutions and ointments in the treatment of persistent open wounds in humans (39). During the late 1940s and 1950s, a series of largely uncontrolled studies in patients with slow-healing wounds, such as vascular ulcers and pressure (decubitus) ulcers, reported that the application of topical SCC promoted healing more effectively than other commonly used treatments (40, 41). In the late 1950s, SCC was added to papain and urea-containing ointments used for the chemical debridement of wounds in order to reduce local inflammation, promote healing, and control odor (33). SCC-containing papain/urea ointments are still available in the US by prescription (42). Several studies have reported that such ointments are effective in wound healing (43). A spray formulation of the papain/urea/SCC therapy is also available (44).

Skin conditions

A few small studies have investigated SCC as a topical treatment for various skin conditions. In a pilot study of 10 adults (ages 18-30 years) who had mild-to-moderate acne vulgaris and enlarged facial pores, twice daily application of a 0.1% liposomal SCC gel for three weeks improved a number of clinical parameters of the Global Acne Assessment Scale (i.e., facial oiliness, facial blotchiness, presence and size of facial pores, and number of acne lesions) compared to baseline (45). Additionally, a pilot study in 10 women (ages 40 years or older) with noticeable photodamage and solar lentigines found that twice daily topical application of a gel containing 0.66% SCC complex salts for eight weeks improved various clinical measures, including tactile and visual roughness of facial skin, skin radiance, fine lines, pore size, and overall photodamage (46). A few case reports have also observed some improvement in facial redness and rosacea with application of topical SCC (47).

While the reports from these studies are interesting, placebo-controlled clinical trials are needed to determine whether SCC may have utility in treating various skin conditions.

Sources

Chlorophylls

Chlorophylls are the most abundant pigments in plants, with chlorophyll a being two to four times as prevalent as chlorophyll b (6, 48). Dark-green leafy vegetables like spinach are rich sources of natural chlorophylls. The chlorophyll content of selected vegetables are presented in **Table 1** (49).

Table 1. Chlorophyll Content of Selected Raw Vegetables

Food	Serving	Chlorophyll (mg)
Spinach	1 cup	23.7
Parsley	½ cup	19.0
Cress, garden	1 cup	15.6
Green beans	1 cup	8.3
Arugula	1 cup	8.2
Leeks	1 cup	7.7
Endive	1 cup	5.2
Sugar peas	1 cup	4.8
Chinese cabbage	1 cup	4.1

Food and supplements

Chlorophyll

Green algae like chlorella are often marketed as supplemental sources of chlorophyll. Because natural chlorophyll is not as stable as SCC and is much more expensive, most over-the-counter chlorophyll supplements actually contain sodium copper chlorophyllin.

Sodium copper chlorophyllin

Oral preparations of sodium copper chlorophyllin (also called chlorophyllin copper complex) are available as a dietary supplement and as an over-the-counter drug (Derifil) used to reduce odor from colostomies and ileostomies, or to reduce fecal odor due to incontinence (50). Oral doses of 100 to 300 mg/day in three divided doses have been used to control fecal and urinary odor (see Therapeutic Uses of Chlorophyllin).

In the US, SCC is found in minor quantities in some types of green table olives (51). It is also approved for use as a green color additive in a limited number of foods like chewing gum (52), as well as in drugs and cosmetics, as detailed in the Code of Federal Regulations 21 (53).

Zinc chlorophyll derivatives

In US supermarkets, canned green beans thermally processed in a zinc chloride solution to produce zinc chlorophyll derivatives within the green beans themselves are sold under the trademarked name "veri-green" (54). Because zinc chlorophyll derivatives are more robust to heat and acid treatment, they better retain a bright green color as compared to native magnesium-bound chlorophyll (48).

Safety

Natural chlorophylls are not known to be toxic, and no toxic effects have been attributed to chlorophyllin despite more than 50 years of clinical use in humans (11, 33, 39). When taken orally, supplemental chlorophyll or sodium copper chlorophyllin may cause green discoloration of urine or feces, or yellow or black discoloration of the tongue (55). There have also been occasional reports of diarrhea related to oral SCC use. When applied topically to wounds, SCC has been reported to cause mild burning or itching in some cases (56). Oral chlorophyllin may result in false positive results on guaiac card tests for occult blood (57). Since the safety of chlorophyll or chlorophyllin supplements has not been tested in pregnant or lactating women, they should be avoided during pregnancy and lactation.

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Food and Beverages

Plant-based foods, including fruit, vegetables, legumes, whole grains, and nuts, are prominent features of healthy dietary patterns. In addition to providing energy and essential micronutrients, plant-based foods contribute thousands of biologically active phytochemicals (plant chemicals that may affect health) to the human diet. While there is ample evidence to support the health benefits of diets rich in fruit, vegetables, legumes, whole grains, and nuts, evidence that these effects are due to specific nutrients or phytochemicals is limited. Although scientists are very interested in the potential for specific phytochemicals to prevent or treat disease, current scientific evidence suggests that plant-based foods are the healthiest phytochemical delivery system.

- Fruit and Vegetables
- Cruciferous Vegetables
- Garlic
- Legumes
- Nuts
- Whole Grains
- Glycemic Index and Glycemic Load
- Coffee
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Fruit and Vegetables

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日本語

Summary

- Dietary patterns characterized by high intakes of fruit and vegetables are consistently associated with lower risks of cardiovascular disease and type 2 diabetes mellitus. *(More information)*
- Although prospective cohort studies provide weak support for an association between total fruit and vegetable consumption and cancer risk, they provide some evidence that high intakes of certain classes of fruit or vegetables are associated with reduced risk of individual cancers. *(More information)*
- Most observational studies suggest that diets rich in fruit and vegetables may have beneficial effects on bone health during aging. Yet, large randomized controlled trials are needed to confirm such benefits. *(More information)*
- Adherence to diets rich in fruit and vegetables has been associated with a lower risk of age-related macular degeneration (AMD), a leading cause of blindness in older people. Randomized controlled trials found supplementation with carotenoids — compounds found in fruit and vegetables — may delay the progression to advanced AMD in subjects with the disease. *(More information)*
- Oxidative stress and inflammation play key roles in the etiology of chronic obstructive lung disease (COPD). Current evidence suggests that fruit and vegetables high in antioxidants like vitamin C, β-carotene, or flavonoids could play a protective role against COPD. *(More information)*
- Regular consumption of fruit and vegetables may reduce risk of some chronic diseases, thereby improving overall health and longevity. *(More information)*
- The 2015-2020 Dietary Guidelines for Americans recommend consuming a healthy diet that includes, among other things, a variety of vegetables from all of the subgroups and fruit. *(More information)*

Introduction

Despite disagreements regarding the optimal components of a healthy diet, the importance of fruit and vegetables is rather undisputed. The results of numerous epidemiological studies provide consistent evidence suggesting associations between diets rich in fruit and vegetables and lower risks of chronic disease. On the other hand, evidence that very high doses of individual micronutrients or phytochemicals found in fruit and vegetables can provide similar health benefits is inconsistent and relatively weak. In addition to essential micronutrients, fruit and vegetables contain thousands of biologically active phytochemicals that are likely to interact in a number of ways to prevent disease and promote health (1). Fruit and vegetables are rich in antioxidants, which help protect the body from oxidative damage induced by pro-oxidants. The best way to take advantage of these complex interactions is to eat a variety of fruit and vegetables.

Disease Prevention

Cardiovascular disease

Prospective cohort studies have consistently reported inverse associations between high intakes of fruit and vegetables and risk of cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke (2-4). A 2017 meta-analysis of prospective cohort studies found a 16% lower risk of CVD with high versus low fruit and vegetable intake and an 8% lower risk with every 200 grams (g)/day increment in daily fruit and vegetable intake in a dose-response analysis (2). Similar risk reductions were reported for daily 200-g increments in fruit and/or vegetable intake and risks of CHD and stroke (2). However, regarding primary CVD prevention in high-risk subjects, evidence that increasing intakes of fruit and vegetable can improve cardiovascular risk factors is scarce because of a lack of long-term intervention studies (5). In a small 12-week intervention study in 109 overweight adults at high risk for CVD, no differences in blood pressure and serum concentrations of low-density lipoprotein (LDL)-cholesterol and C-reactive protein (CRP; a marker of inflammation) were found between participants consuming two (~160 g), four (~320 g), or seven (~560 g) daily servings of fruit and vegetables (6).

Nonetheless, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes fruit, vegetables, whole grains, poultry, fish, nuts, and low-fat dairy, was found to substantially lower systolic/diastolic blood pressures by 11.4/5.5 mm Hg in hypertensive and 3.5/2.1 mm Hg in normotensive people compared to a typical US diet (for additional information on the DASH diet, see the National Institutes of Health website) (7). Blood pressure lowering effectively reduces CVD risk (8). Adherence to a Mediterranean-style dietary pattern, also characterized by high fruit and vegetable intake, might further contribute to preventing cardiovascular events in healthy and high-risk subjects through normalizing total and LDL-cholesterol concentrations in the circulation (9).

A number of compounds may play a part in the cardioprotective effects of fruit and vegetables, including vitamin C, folate, potassium, fiber, and various phytochemicals (10, 11). However, supplementation with individual micronutrients or phytochemicals has not generally resulted in significantly decreased incidence of cardiovascular events in randomized controlled trials. Thus, in the case of fruit and vegetables, the benefit of the whole may be greater than the sum of its parts. Of note, the World Health Organization (WHO) recommends the daily consumption of >400 g of fruit and vegetables as part of a healthy diet low in fat, sugar, and salt (sodium chloride), in order to minimize the risk of certain non-communicable diseases like CVD and type 2 diabetes mellitus (12).

Type 2 diabetes mellitus

Nearly 10% of the US population is affected by type 2 diabetes mellitus and another 34% has impaired glucose control (prediabetes) that places them at high risk of developing type 2 diabetes (13). Adherence to a Mediterranean-style or Dietary Approaches to Stop Hypertension (DASH) diet — both rich in vegetables, legumes, fruit, and nuts — has been associated with a lower risk of developing type 2 diabetes (14). Yet, a recent meta-analysis of prospective cohort studies failed to find any association between intakes of vegetables, legumes, fruit, or nuts and the risk of type 2 diabetes (15). In contrast, high intakes of whole-grain and dairy foods were linked to a lower risk of type 2 diabetes, while consumption of sugar-sweetened beverages and red and processed meat were associated with an increased risk of diabetes (15). Whether evidence for a potential protective effect of fruit and vegetables regarding type 2 diabetes is more easily detectable when they are combined with other food groups within a diet rather than when their effect is singled out is unclear. A recent meta-analysis of 12 cross-sectional and two prospective cohort studies found a 27% lower risk of type 2 diabetes with the consumption of a vegetarian diet (16). Yet, it is unclear whether the potential benefit of such a diet is linked to the fact that it does not include foods that are associated with a higher diabetes risk (i.e., red and processed meat) and/or because of the inclusion of foods like fruit and vegetables that may be protective. Nevertheless, in the European Prospective Investigation into Cancer and nutrition (EPIC)-Norfolk, a prospective study that followed 3,704 participants for nearly 11 years, a lower risk of type 2 diabetes was linked to higher intakes of vegetables (but not fruit), as well as with a greater diversity of consumed fruit and vegetables (17). A dose-response analysis found an 8% lower risk of diabetes with every increase of two items added to the variety of fruit or vegetables consumed each week (17). A follow-up study also showed that a composite score reflecting fruit and vegetable consumption, derived from circulating concentrations of vitamin C, β-carotene, and lutein, was also inversely associated with the risk of type 2 diabetes in this cohort (18).

Without changes in lifestyle behavior, especially regarding dietary habits and physical activity, individuals with prediabetes will eventually progress to develop overt type 2 diabetes. Strategies promoting healthier eating habits to improve glucose control usually encourage the consumption of more fruit and vegetables and the concomitant reduction of sugar and fat intake. The American Diabetes Association does not specifically emphasize an increase in fruit and vegetable intake for diabetes prevention yet recommends dietary strategies that include reducing caloric and fat intake, as well as increasing intake of whole-grain foods and dietary fiber that can be sourced in fruit and vegetables (19).

Cancer

A plethora of observational studies has investigated the relationship between intakes of fruit and vegetables and risk of developing site-specific cancers. A 2014 report summarized the findings of 27 studies that examined fruit and vegetable consumption in relation to incidental cancer in participants of the ongoing, multicenter European Prospective Investigation into Cancer and nutrition (EPIC) study (20). This report found the highest versus lowest quintile of fruit intake (≥356 g/day vs. ≤89 g/day) to be associated with a 40% lower risk of oropharyngeal, laryngeal, and esophageal cancers and a 20% lower risk of lung cancer. No associations were observed between fruit intake and cancers of the lymphatic system, stomach, pancreas, breast, cervix, prostate, or bladder. There were also no inverse associations between intakes of vegetables and risk of cancer. More recently published EPIC data analyses also failed to find significant inverse associations between fruit and/or vegetable intakes and risk of hepatocellular carcinoma (21), colorectal cancer (22), hormone-receptor-positive breast cancer (23), or differentiated thyroid carcinoma (24). Further, mixed results from recent meta-analyses of observational studies are reported in **Table 1**, with significant associations noted in bold. Some of the discrepancies might be attributed to study design. Compared to prospective cohort studies, which collect dietary information from participants before they are diagnosed with cancer, retrospective case-control studies are more susceptible to bias in the selection of participants (cases and controls) and with dietary recall (25). For example, this might explain why fruit intake is associated with the risk of esophageal adenocarcinoma in the meta-analysis of six case-control studies but not in that of three cohort studies in the meta-analysis by Li et al. (26). Inaccurate measurements (introducing measurement bias) and changes in the diet during follow-up in prospective cohort studies may also contribute to reporting associations that are proven spurious or to missing true associations. A 2012 meta-analysis of prospective studies suggested that, when compared to direct measurements of plasma carotenoids, the use of a food-frequency questionnaire to assess carotenoid intake introduced measurements errors that led to underestimating the strength of the association between carotenoid intake and reduced breast cancer risk (27).

Table 1. Fruit & Vegetable Intake and Cancer Risk: Meta-analyses of Observational Studies

Type of Cancer	References	Highest versus Lowest Quantile of Intake	Type of Observational Studies	Risk Ratio [RR] or Odds Ratio [OR] (95% Confidence Interval)*
All cancer types	Aune et al. (2017) (2)	Total fruit & vegetables	14 prospective cohort studies	**RR: 0.97 (0.95-0.99)**
		Vegetables	19 prospective cohort studies	**RR: 0.96 (0.93-0.99)**
		Cruciferous vegetables	5 prospective cohort studies	**RR: 0.84 (0.72-0.97)**
		Green yellow vegetables	5 prospective cohort studies	RR: 0.88 (0.77-1.00)
		Fruit	25 prospective cohort studies	**RR: 0.96 (0.94-0.99)**
		Citrus fruit	5 prospective cohort studies	RR: 0.97 (0.90-1.04)
Bladder cancer	Vieira et al. (2015) (28)	Total fruit & vegetables	9 prospective cohort studies	RR: 0.89 (0.75-1.05)
		Vegetables	10 prospective cohort studies	RR: 0.92 (0.84-1.01)
		Cruciferous vegetables	7 prospective cohort studies	RR: 0.85 (0.69-1.06)
		Leafy vegetables	6 prospective cohort studies	RR: 0.90 (0.78-1.04)

		Fruit	12 prospective cohort studies	RR: 0.91 (082-1.00)
		Citrus fruit	8 prospective cohort studies	**RR: 0.87 (0.76-0.99)**
	Liu et al. (2015) (29)	Vegetables	14 case-control studies	RR: 0.76 (0.58-1.00)
			10 prospective cohort studies	RR: 0.92 (0.84-1.02)
		Fruit	15 case-control studies	**RR: 0.76 (0.66-0.88)**
			12 prospective cohort studies	**RR: 0.85 (0.73-0.98)**
Breast cancer	Aune et al. (2012) (30)	Total fruit & vegetables	6 prospective cohort studies	**RR: 0.89 (0.80-0.99)**
		Vegetables	9 prospective cohort studies	RR: 0.99 (0.92-1.06)
		Fruit	10 prospective cohort studies	**RR: 0.92 (0.86-0.98)**
Colorectal adenoma	Ben et al. (2015) (31)	Total fruit & vegetables	5 case-control and 3 prospective cohort studies	**RR: 0.82 (0.75-0.91)**
		Vegetables	12 case-control and 5 prospective cohort studies	RR: 0.91 (0.80-1.02)
		Fruit	15 case-control and 5 prospective cohort studies	**RR: 0.94 (0.92-0.97)**
Colorectal cancer	Aune et al. (2011) (32)	Total fruit & vegetables	11 prospective cohort studies	**OR: 0.92 (0.86-0.99)**
		Vegetables	16 prospective cohort studies	**OR: 0.91 (0.86-0.96)**
		Fruit	14 prospective cohort studies	**OR: 0.90 (0.83-0.98)**
	Kashino et al. (2015) (33)	Vegetables	9 case-control studies	**OR: 0.75 (0.59-0.96)**
			6 prospective cohort studies	RR: 1.00 (0.92-1.10)
Esophageal adenocarcinoma	Li et al. (2014) (26)	Total fruit & vegetables	4 case-control studies	**RR: 0.61 (0.44-0.84)**
		Vegetables	6 case-control studies	RR: 0.75 (0.53-1.06)
			3 prospective cohort studies	RR: 0.76 (0.54-1.05)
		Fruit	6 case-control studies	**RR: 0.59 (0.38-0.90)**
			3 prospective cohort studies	RR: 0.99 (0.72-1.36)
Esophageal cancer	Vingeliene et al. (2016) (34)	Citrus fruit	5 studies with a prospective design[#]	**RR: 0.85 (0.73-0.99)**
Gastric cancer	Wang et al. (2015) (35)	Vegetables	19 prospective cohort studies	RR: 0.96 (0.88-1.06)
		Fruit	22 prospective cohort studies	**RR: 0.90 (0.83-0.98)**
	Bae et al. (2016) (36)	Citrus fruit	5 prospective cohort studies	**RR: 0.87 (0.76-0.99)**
	Vingeliene et al. (2016) (34)	Citrus fruit	4 studies with a prospective design[#]	RR: 0.93 (0.82-1.07)
Hepatocellular carcinoma	Yang et al. (2014) (37)	Vegetables	9 case-control studies	RR: 0.76 (0.48-1.20)
			8 prospective cohort studies	**RR: 0.66 (0.51-0.86)**
		Fruit	19 case-control studies	**RR: 0.77 (0.67-0.88)**
			19 prospective cohort studies	**RR: 0.84 (0.75-0.94)**
Lung cancer	Wang et al. (2015) (38)	Vegetables	19 case-control studies	**RR: 0.62 (0.54-0.70)**
			18 prospective cohort studies	**RR: 0.88 (0.81-0.97)**
		Fruit	19 case-control studies	**RR: 0.77 (0.67-0.88)**
			19 prospective cohort studies	**RR: 0.84 (0.75-0.94)**
	Vieira et al. (2016) (39)	Total fruit and vegetables	18 studies with a prospective design[#]	**RR: 0.86 (0.78-0.94)**
		Vegetables	25 studies with a prospective design	**RR: 0.92 (0.87-0.97)**
		Cruciferous vegetables	11 studies with a prospective design	**RR: 0.87 (0.79-0.97)**
		Green leafy vegetables	9 studies with a prospective design	**RR: 0.85 (0.75-0.96)**
		Fruit	29 studies with a prospective design	**RR: 0.82 (0.76-0.89)**
		Citrus fruit	15 studies with a prospective design	**RR: 0.85 (0.78-0.93)**

*Statistically significant associations noted in bold.
[#] Cohort, nested case-control, and case-cohort studies

Additional evidence from observational studies, discussed in MIC articles focusing specifically on cruciferous vegetables, garlic, carotenoid-rich vegetables, and legumes suggests that high intakes of certain classes of vegetables are associated with reduced risk of individual cancers. The 2007 report from the World Cancer Research Fund International (WCRF)/American Institute for Cancer Research (AICR) concluded that fruit and non-starchy vegetables were probably protective against some cancers, recommending a daily consumption of five portions (400 g; based on an average portion weighing 80 g) of a variety of vegetables and fruit (40). AICR continuously collates evidence from cohort and randomized controlled studies through its Continuous Update Project (CUP), and updated CUP-derived Cancer Prevention Recommendations are expected to be published in late 2017 (41).

Osteoporosis

Bone turnover

Fruit and vegetables are rich in precursors of bicarbonate ions (HCO$_3^-$), which serve to buffer acids in the body. When the quantity of bicarbonate ions is insufficient to maintain normal pH, the body is capable of mobilizing alkaline calcium salts from bone in order to neutralize acids consumed in the diet and generated by metabolism (42). It has been hypothesized that higher consumption of fruit and vegetables could help reduce the net acid content of the diet and preserve calcium in bones, which might otherwise be mobilized to maintain normal pH to the detriment of bone health. Results from the ancillary DASH-Sodium study, which emphasizes the intake of fruit, vegetables, whole-grain foods, and low-fat dairy, supported a beneficial link between bone health and fruit and vegetable intake. Compared to a control diet, one month-administration of the DASH diet to (pre)hypertensive middle-aged adults significantly lowered the rate of bone turnover, as shown by reduced serum concentrations of osteocalcin (OC), a marker of bone formation released by osteoblasts into circulation during the mineralization of newly synthesized collagen. C-terminal telopeptide of type 1 collagen (CTX) — a marker of bone resorption released from bone collagen into circulation following bone degradation by osteoclasts — was also decreased (43). However, more recent randomized controlled interventions found no effect of increasing fruit and vegetable intake on markers of bone turnover (44-46). The results of a placebo-controlled trial in 276 healthy postmenopausal women suggested that supplementing the diet with alkali, either through supplemental potassium citrate or an additional 300 g/day of fruit and vegetables, did not reduce bone turnover, increase bone mineral density (BMD), or blunt the age-associated bone loss over a two-year period (45). The effect of five portions of fruit and vegetables on measures of dietary acid/base balance and bone turnover markers was also reported as a secondary outcome in the Ageing and Dietary Intervention Trial that included 83 healthy older participants (ages, 65-85 years) (46). Compared to habitual fruit and vegetable intakes of ≤2 portions/day, the consumption of five portions per day for 16 weeks increased the alkalinity of the diet but failed to reduce markers of bone turnover (46). There were also no significant reductions in circulating bone turnover markers in postmenopausal women with osteopenia supplemented with six extra servings of fruit and vegetables per day (~400 g/day) for 12 weeks (44).

Bone mineral density

Several observational studies have examined intakes of fruit and vegetables in relation to bone mineral density (BMD) in men and women, providing mixed results (reviewed in 47). In an early cross-sectional analysis of the longitudinal Framingham Osteoporosis Study in elderly adults (mean age, 75 years), baseline intakes of fruit and vegetables were positively associated with BMD at various sites, including trochanter, femoral neck, and radius (48). Baseline fruit and vegetable intakes were also positively associated with longitudinal changes of trochanter BMD over four years in elderly men but not elderly women (48, 49). Two recent cross-sectional studies in Chinese cohorts reported positive relationships between BMD and intakes of fruit rather than vegetables (50, 51). In the cross-sectional analysis of two Hong-Kong-based cohorts of 3,995 older participants (≥65 years), higher daily intakes of fruit — but not vegetables — were associated with significantly higher whole-body and femoral neck BMD in men and women (50). The cross-sectional study of 3,089 Chinese adults (ages, 40-75 years) reported positive associations between whole-body, total hip, and femoral neck BMD and higher intakes of apples, pears, peaches, pineapples, plums, and to a lesser extent, citrus fruit (51). However, the two-year supplementation of 300 g/day of fruit and vegetables failed to reduce BMD loss in healthy postmenopausal women (45).

Risk of fracture

A pooled analysis of data from several prospective cohort studies, including the EPIC-Elderly Greece (9,534 participants), EPIC-Elderly Sweden (3,276 participants), Cohort of Swedish Men (COSM; 20,150 men), Swedish Mammography Cohort (SMC; 17,506 women), and Nurses' Health Study (NHS; 91,552 women), found a 39% higher risk of hip fracture with intakes of fruit and vegetables ≤1 serving/day compared to 4-5 daily servings (52). Further subgroup analysis linked higher hip fracture risk specifically with low intakes of vegetables rather than fruit. Finally, compared to 4-5 daily servings of fruit and vegetables, there was no reduction in hip fracture risk with intakes greater than 5 servings/day (52). The consumption of fruit and vegetables has been recently examined in relation to 415 fracture-related hospitalizations identified during a 14.5-year follow-up of 1,468 elderly participants (≥70 years) of the Perth Longitudinal Study of Aging in Women (PLSAW) (53). Whereas no association was found between fruit intakes and fracture risk, high versus low intake of total vegetables (≥3 servings/day versus <2 servings/day) was associated with a 27% reduced risk of all fractures and a 39% reduced risk of hip fractures. Further analyses suggested an inverse association between consumption of allium vegetables (onion, leek, and garlic) and risk of fracture (53).

Although observational studies suggest a positive relationship between diets rich in fruit and vegetables and bone health during aging, randomized controlled studies are needed to examine the nature of this association.

Eye diseases

Cataracts

Cataracts are thought to be caused by oxidative damage of proteins in the eye's lens induced by long-term exposure to ultraviolet (UV) light (54). The resulting cloudiness and discoloration of the lens leads to vision loss that becomes more severe with age. A 2015 meta-analysis of nine observational studies found a 28% lower risk of age-related cataracts with the highest versus lowest intakes of vegetables (55). In a large Swedish prospective study that followed 30,607 middle-aged and elderly women for a mean 7.7 years, the risk of age-related cataracts has been examined in relation to the estimated total antioxidant capacity of the diet (56). Higher versus lower estimates of total dietary antioxidant capacity were associated with a 13% lower risk of cataracts. Subgroup analyses showed that this inverse association was statistically significant in women younger than 65 years and in corticosteroid users (56). Pooled analyses of observational studies that investigated the relationships between individual nutrients with antioxidant properties and the risk of cataracts have also suggested a lower risk of cataracts with higher intakes or higher blood concentrations of vitamin C, vitamin A, or β-carotene, although the results vary according to study design (i.e., case-control versus cross-sectional versus longitudinal) (57, 58). However, a 2012 review of nine randomized clinical trials found no substantial effect of β-carotene, vitamin C, and vitamin E, administered individually or in combination over 2.1 to 12 years, on the risk of cataracts or cataract surgery (59). In addition, a large randomized controlled trial in 5,802 subjects at high risk for cardiovascular disease recently reported no difference in cataract surgery incidence over a seven-year follow-up period between participants assigned to a Mediterranean diet that included the whole range of antioxidant nutrients and those assigned to a control diet (60). A secondary analysis reported a 29% lower cataract surgery risk in participants in the highest versus lowest tertile of vitamin K$_1$ intake (61).

Age-related macular degeneration

In industrialized countries, degeneration of the macula, located in the center of the retina, is the leading cause of blindness in older adults (62). Long-term light exposure and oxidative damage in the outer segments of photoreceptors may lead to drusen and/or pigment abnormalities in the macula, increasing the risk of age-related macular degeneration (AMD) and central blindness.

Several recent observational studies have examined AMD prevalence, incidence, progression, or severity in relation to dietary patterns. Most of them used constructed scoring systems reflecting the level of adherence to specific dietary patterns by individuals. The European Eye (EUREYE) study examined associations between the prevalence of AMD and dietary patterns among 4,753 individuals from seven European countries. Adherence to the Mediterranean diet was assessed using a Mediterranean Diet Score system that captured high intakes of key food items, such as olive oil, wine, fruit, vegetables or salad, fish, and legumes, and low intakes of meat. High adherence to the Mediterranean Diet was associated with a reduced risk of developing large drusen, but there was no association with the risk of early or advanced AMD (63). In the Carotenoids in the Age-Related Eye Disease Study (CAREDS) that included 1,313 US women (ages, 50-79 years), high adherence to a Mediterranean-like dietary pattern characterized by high intakes of fruit, vegetables, whole grains, legumes, nuts, and fish, and moderate intakes of red meat and alcohol, were found to be associated with a 66% lower risk of early AMD (64). This Mediterranean-like dietary pattern, which is closer to dietary patterns occurring in the US, was also associated with a 26% lower risk of progression to advanced AMD in 2,525 subjects followed for a mean 8.7 years in the Age-Related Eye Disease Study (AREDS) (65). Of note, this association was no longer valid when the analysis was restricted to individuals with a genetically determined susceptibility to AMD, i.e., those homozygous for the risk allele of the *complement factor H [CFH]* gene (rs1410996) (65). A cross-sectional study that analyzed baseline data from 4,088 AREDS participants, among whom 2,739 had no AMD, 4,599 had early AMD, and 765 had advanced AMD, identified two main dietary patterns: so-called "Oriental" and "Western" patterns (66). High adherence to the "Oriental" dietary pattern characterized by consumption of vegetables, legumes, fruit, fish, whole grains, poultry, and low-fat dairy products was associated with lower risks of early and advanced AMD. In contrast, higher risks of early and advanced AMD were found in individuals with high adherence to a "Western" diet that included red and processed meat, potatoes, French fries, butter, high-fat dairy products, eggs, refined grains, and sweets and desserts (66).

Among observational studies that focused on individual food groups or nutrients, some have suggested that high intakes of fruit, vegetables, or antioxidant nutrients, such as vitamin C, vitamin E, and carotenoids, might be protective against AMD. In two early case-control studies, high intakes of dark-green leafy vegetables especially rich in lutein and zeaxanthin, two carotenoids present in the retina, were associated with a significantly lower risk of developing AMD (67, 68). In a prospective cohort study of more than 118,000 men and women, those who consumed ≥3 servings/day of fruit had a 36% lower risk of developing AMD over the next 12 to 18 years than those who consumed <1.5 servings/day (69). Interestingly, vegetable intake was not associated with the risk of AMD in this cohort. Another study combining lutein and zeaxanthin intake was not associated with the prevalence of intermediate AMD in a cohort of women aged 50-79 years (70). However, further analysis of the data revealed that women younger than 75 years with stable intakes of lutein and zeaxanthin had a 43% lower risk of developing intermediate AMD (70). In the AREDS trial, oral supplementation with β-carotene (15 mg/day), vitamin C (500 mg/day), vitamin E (400 IU/day), zinc (80 mg/day as zinc oxide), and copper (2 mg/day as cupric oxide) for five years was shown to reduce the risk of developing advanced AMD by 25% (71). In a follow-up study — the AREDS2 trial — supplemental lutein (10 mg/day) and zeaxanthin (2 mg/day) in combination with the 'AREDS formulation' only reduced the risk of progression to late AMD in the subset of participants with the lowest dietary intakes of lutein and zeaxanthin (72). A more detailed account of the epidemiological evidence regarding the relationship between dietary and supplemental carotenoids and AMD risk can be found in the article on Carotenoids.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a condition that combines emphysema and chronic bronchitis, two chronic lung conditions that are characterized by airway obstruction. Smoking and indoor/outdoor pollution are considered to be primary contributors to COPD development, but dietary patterns low in fruit and vegetables and providing inadequate vitamin intakes may also affect lung function and risk for COPD (reviewed in 73, 74). Early observational studies in Europe indicated that higher fruit intakes, especially apple intakes, were associated with higher spirometric values (including forced expiratory volume in 1 second [FEV1]), indicative of better lung function (75-77). In a cross-sectional study of 2,500 middle-aged Welsh men, slower declines in lung function were associated with the consumption of at least five apples weekly compared to no consumption (76). Another study of 2,917 European men followed over 20 years found that each 100 g (3.5 oz) increase in daily fruit consumption was associated with a 24% lower risk of COPD-related mortality (78). Additionally, when compared to a Western dietary pattern of refined grains, cured and red meats, French fries, and desserts, a prudent diet emphasizing fruit, vegetables, fish, and whole grains was associated with a 25%-50% lower risk of COPD in two large cohorts of men (79) and women (80). In a large prospective cohort study that followed 44,335 Swedish men (mean age, 60.2 years) for a mean 13.2 years, the highest versus lowest quintile (≥5.3 servings/day versus <2 servings/day) of fruit and vegetable intakes was associated with a 35% lower risk of developing COPD (81). Subgroup analyses showed that fruit and vegetable intakes were inversely associated with COPD risk in current and former smokers, but not in men who never smoked. Because oxidative stress and inflammation play key roles in the etiology of chronic obstructive lung disease, it has been suggested that fruit and vegetables high in antioxidants, such as vitamin C, β-carotene, or flavonoids, could play a protective role against COPD. A three-year randomized controlled study in 120 patients with COPD (mean age, 68.1 years) assigned to a diet rich in antioxidants, such as fresh fruit, fruit juice, and vegetables, or a control diet has provided support for the antioxidant hypothesis (82). Shifting to a higher consumption of fruit and vegetables prevented the decline of lung function observed in subjects who consumed the control diet (82).

Asthma

Environment and lifestyle changes, including shifts toward unhealthy diets, are thought to contribute to the increasing prevalence of asthma and allergic diseases in industrialized countries. Observational studies that examined asthma and allergic symptoms in relation to fruit and vegetable intakes have provided mixed results (83). A cross-sectional analysis of a population-based study in 32,644 Portuguese adults identified five dietary patterns, of which one included fish, fruit, and vegetables — three essential components of the Mediterranean diet. This dietary pattern was found to be inversely associated with self-reported asthma symptoms and self-reported use of asthma drugs — yet not with self-reported medical diagnosis of asthma (84). In contrast, the most recent cross-sectional study of 3,202 participants in the European Global Allergy and Asthma Network of Excellence (GA^{2}LEN) showed no association between fruit and vegetable intake and risk of asthma and chronic rhino-sinusitis (85). A 2017 systematic review identified 58 studies (in addition to the two above-cited studies) reporting fruit and vegetable intake in relation to lung function, wheeze, or asthma, of which 30 were cross-sectional studies and 41 conducted in children and/or adolescents (83). A majority of studies (8 in adults and 22 in children) reported inverse associations between diets high in fruit and vegetables and risk of asthma and/or wheeze: 20 studies (8 in adults and 12 in children) showed that intakes of either fruit or vegetables were inversely associated with asthma and/or wheeze, and eight studies (one in adults and seven in children) found no associations. Pooled data analyses showed an inverse association between vegetable intake and risk of asthma, as well as fruit intake and asthma severity and risk of wheeze (83). A previous meta-analysis of observational studies reported lower risks of wheeze and asthma with higher intakes of fruit and vegetables in adults and children in cross-sectional studies, but not all prospective cohort studies have supported these findings (86). Subgroup analyses also suggested inverse associations between intakes of apples, citrus fruit, and tomatoes and risks of wheeze and asthma. Finally, pooled analyses of prospective cohort studies have revealed no association between fruit or vegetable intake during pregnancy and risk of wheeze or asthma in the offspring (86).

Cognitive decline and neurodegenerative disease

Observational studies

Results from most cross-sectional and longitudinal studies suggest that diets rich in fruit and vegetables might help prevent age-related cognitive deterioration and reduce the risk of neurodegenerative diseases like Alzheimer's disease (AD) (87). A 2014 systematic review identified 11 prospective cohort studies (88), of which four examined fruit and vegetable intakes in relation to incidence of neurodegenerative diseases. All four prospective studies reported inverse associations between consumption of fruit and vegetables and risk of developing mild cognitive impairments or dementia, including AD (89-92). Among the seven prospective cohort studies positively linking fruit and vegetable intakes to better cognitive performance (reviewed in 88), a two-year follow-up of 13,388 women (mean age, 74 years) in the Nurses' Health Study (NHS) found less cognitive decline in those in the highest versus lowest intakes of green leafy vegetables, cruciferous vegetables, and legumes (93). Fruit consumption was not associated with changes in cognitive performance in this study (93). However, a more recently published NHS study in 16,010 women analyzed intakes of major flavonoid-containing foods in relation to cognitive test scores and reported less cognitive decline with higher long-term intakes of strawberries and blueberries (94). Finally, a meta-analysis of 13 prospective cohort studies showed better global cognition in healthy older adults consuming the Mediterranean diet compared to control diets. In contrast, there were no differences in measures of episodic, semantic, and working memory between diets (95).

Dietary interventions

To date, only a few interventions have examined the overall effect of fruit- and vegetable-rich diets on cognition in cognitively healthy older adults. One trial assessed cognitive changes in 334 older adults (mean age, 66.9 years) at high risk for cardiovascular disease (CVD) randomly assigned to either a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a control diet (96). Following a median of 4.1 years, both Mediterranean diets prevented the deterioration of cognitive function that was observed in those ascribed the control diet. Compared to participants in the control diet group, those who followed the Mediterranean diet plus nuts had improved composite cognitive test scores for memory, while those in the Mediterranean diet plus olive oil group had better composite scores for frontal function and global cognition (96). However, in a six-month trial in 137 CVD-free Australian adults (mean age, 72 years), consumption of a Mediterranean diet rich in fruit, legumes, dairy, nuts, olive oil, and seafood did not result in improved cognitive function — measured by a battery of 13 neuropsychological tests — compared to the habitual diet (97, 98).

Mortality

Because regular consumption of fruit and vegetables may reduce the risk of some chronic diseases, it may also improve overall health and longevity. A 2017 meta-analysis of 95 prospective cohort studies found that daily consumption of fruit and vegetables was inversely associated with cause-specific and all-cause mortality (2). The risk of all-cause mortality was found to be 24% lower with five daily serving of fruit and vegetables combined (~400 mg/day) compared to little or no daily intake of fruit and vegetables. Five daily servings of fruit and vegetables were also associated with lower risks of cardiovascular-related (-19%) and cancer-related (-12%) mortality. In addition, the risk of all-cause mortality was lower with higher intakes of specific types of fruit and vegetables. There was evidence of lower risk of all-cause mortality with the highest versus lowest intake level of apples (-20%), berries (-8%), citrus fruit (-10%), cruciferous vegetables (-12%), and green leafy vegetables (-8%). This meta-analysis further reported a reduced risk of all-cause mortality with both cooked (-13%) and raw vegetable (-12%) intakes (2).

Although the Dietary Guidelines for Americans recommend fresh, frozen, and canned fruit equally, the consumption of the latter has been associated with increased risks of all-cause and cardiovascular related mortality in a pooled analysis of three UK-based prospective studies found with consumption of tinned fruit (99). While added sugar content in tinned fruit or exposure to bisphenol A (a chemical component of tin cans) may explain these results, further studies are needed to clarify whether fresh fruit and canned fruit can provide similar health benefits when included as part of a healthy diet.

Finally, although increasing daily intakes of fruit and vegetables would very likely reduce the number of premature deaths caused by cardiovascular disease and cancer in the US population, it is estimated that about 8 in 10 Americans do not meet the current intake recommendations (100).

Intake Recommendations

The 2015-2020 Dietary Guidelines for Americans — issued jointly by the US Department of Health and Human Services and the US Department of Agriculture — recommend to consume a healthy diet which includes, among other things, a variety of vegetables from all of the subgroups and fruit, especially whole fruit (101). In the 2015-2020 Dietary Guidelines for Americans, the unit of measure of a fruit or vegetable serving size is the cup-equivalent (c-eq). In general, one cup-equivalent of fruit corresponds to (1) one cup of cut-up, raw, or canned fruit; (2) one cup (eight fluid ounces) of 100% fruit juice; or (3) one-half cup of dried fruit. **Table 2** provides examples of the size of specific fruit counting as one cup-equivalent.

Table 2. What Counts as One Cup-equivalent of Fruit (adapted from 102)

Fruit	Examples of One Cup-equivalent of Fruit
Apple	1 small
Banana	1 large
Grapefruit	1 medium
Grapes	32 seedless grapes
Peach	1 large
Pear	1 medium
Plum	2 large or 3 medium
Strawberries	8 large berries
100% fruit juice	8 fluid ounces (1 cup)
Dried fruit (e.g., raisins, apricots)	½ cup

One cup-equivalent of vegetables generally corresponds to one cup of raw or cooked vegetables or vegetable juice. One exception is leafy greens (e.g., spinach, romaine, watercress, dark-green leafy lettuce, endive, escarole) for which one cup-equivalent corresponds to one cup of cooked or two cups of raw vegetables. **Table 3** provides specific examples of what counts as one cup-equivalent of vegetables.

Table 3. What Counts as One Cup-equivalent of Vegetables (adapted from 103)

Vegetables	Examples of One Cup-equivalent of Vegetables
Dark-green vegetables	
Greens (e.g., collards, kale)	1 cup, cooked
Raw leafy greens (e.g., watercress, endive, romaine)	2 cups, raw
Spinach	1 cup, cooked 2 cups, raw
Red and orange vegetables	
Carrots	1 cup, chopped, raw or cooked 2 medium 1 cup of baby carrots
Red peppers	1 large pepper
Tomatoes	1 large, raw 1 cup, chopped, raw, canned, or cooked
Sweet potatoes	1 large, baked
Legumes	
Dry beans and peas	1 cup, whole or mashed, cooked
Starchy vegetables	
Corn, yellow or white	1 large ear
White potatoes	1 medium, boiled or baked
Other vegetables	
Celery	1 cup, diced or sliced, raw or cooked 2 large stalks
Green peppers	1 large pepper
Lettuce	2 cups, raw, shredded or chopped
Onions	1 cup, chopped, raw or cooked

The 2015-2020 Dietary Guidelines for Americans provides dietary recommendations, including amounts of fruit and vegetables, designed to meet nutrient needs and Dietary Guidelines standards, for those who choose to follow either a healthy US-style eating pattern, a healthy Mediterranean-style eating pattern, or a healthy vegetarian eating pattern (101). The recommendations are based on estimated energy needs that vary with age, gender, and level of physical activity. Recommended daily intakes of fruit and vegetables at all calorie requirement levels can be found in the '2015-2020 Dietary Guidelines for Americans' report (see Appendices 3-5) (101). **Table 4** provides the amounts of fruit and vegetables (expressed in cup-equivalents) that are recommended at the 2,000-calorie per day level. Regardless of the chosen eating pattern, consumption of a variety of different vegetables and fruit is recommended, including all fresh, frozen, and canned dark-green, red, and orange vegetables, starchy vegetables, legumes (peas and beans), and all fresh, frozen, canned, and dried fruit and 100% fruit juice.

Table 4. 2015-2020 US Dietary Guideline Recommendations for Fruit and Vegetable Intakes*

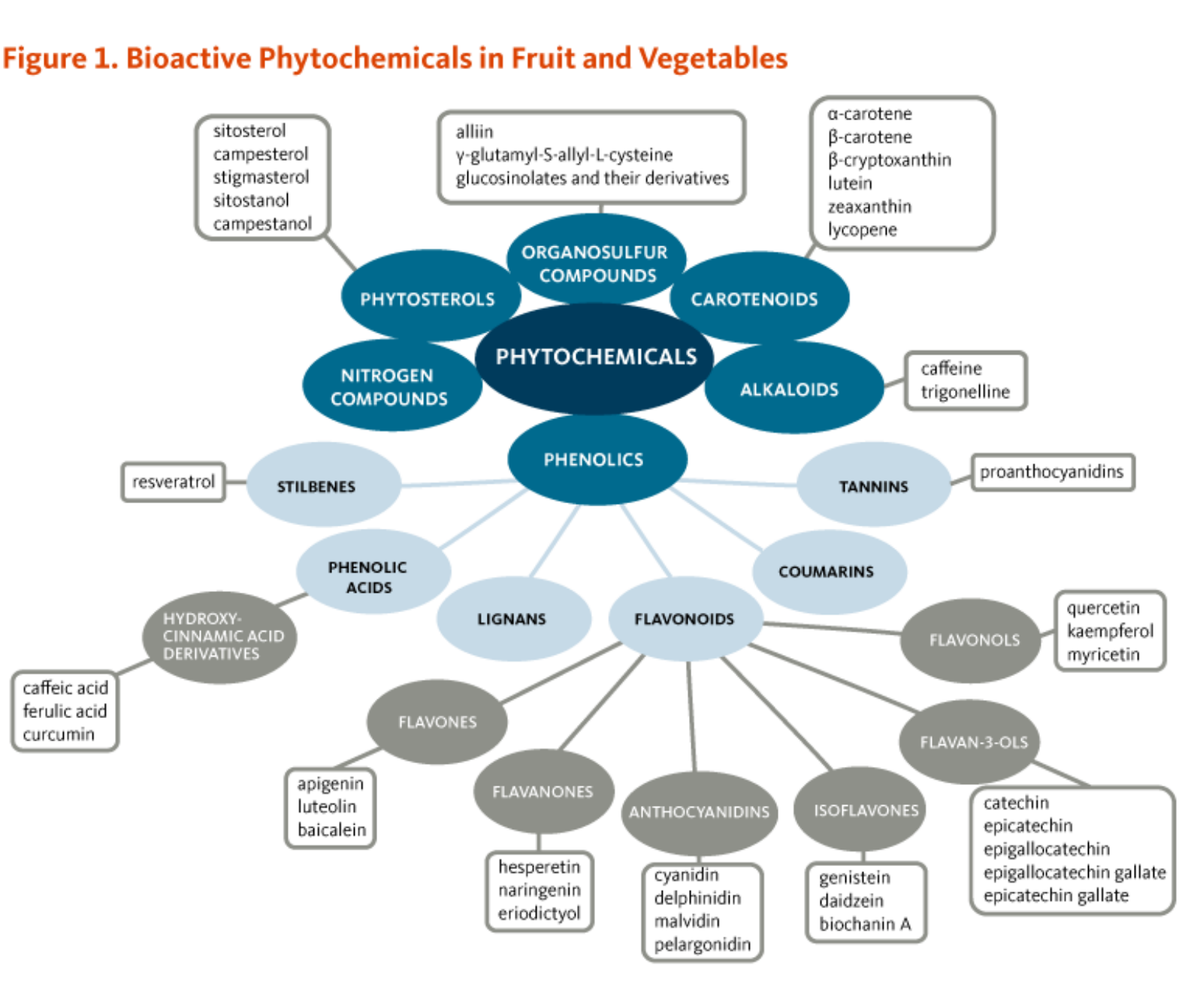
Food	Healthy Eating Patterns		
	US-style	Mediterranean-style	Vegetarian
Vegetables (c-eq/day)	**2½**	**2½**	**2½**
Dark-green vegetables (c-eq/week)	1½	1½	1½
Red and orange vegetables (c-eq/week)	5½	5½	5½
Legumes (c-eq/week)	1½	1½	1½
Starchy vegetables (c-eq/week)	5	5	5
Other vegetables (c-eq/week)	4	4	4
Fruit (c-eq/day)	**2**	**2½**	**2**

*Recommendations for fruit and vegetable intakes at the 2,000-calorie per day level. Estimates of daily calorie needs according to age, gender, and physical activity can be found in the Appendix 2 of the '2015-2020 Dietary Guidelines for Americans' report (101).
c-eq, cup-equivalents

The nonprofit organization, Produce for Better Health Foundation (PBH), has partnered with the US Centers for Disease Control and Prevention (CDC) to develop the Fruits & Veggies — More Matters®health initiative, which aims to help Americans increase their consumption of fruit and vegetables for better health (104). Other initiatives like the US Department of Agriculture (USDA)'s ChooseMyPlate.gov have been developed to help everyone make healthier dietary choices, particularly by adding more fruit and vegetables to daily meals.

Finally, vegetables and fruit not only are a great source of micronutrients, dietary fiber, and unsaturated fat, they also supply a wide range of biologically active phytochemicals (**Figure 1**) that contribute to the health benefits of plant foods. Information regarding the functions and health benefits of specific micronutrients and phytochemicals can be found in articles on vitamins, minerals, and dietary phytochemicals.

Figure 1. Bioactive Phytochemicals in Fruit and Vegetables



[Figure 1 - Click to Enlarge]

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Cruciferous Vegetables

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Summary

- Cruciferous vegetables are unique in that they are rich sources of sulfur-containing compounds known as glucosinolates. *(More information)*
- Chopping or chewing raw cruciferous vegetables results in the formation of bioactive glucosinolate hydrolysis products, such as isothiocyanates and indole-3-carbinol. These metabolites are also generated by colonic bacteria, following the ingestion of cooked cruciferous vegetables. *(More information)*
- The biological activities of glucosinolate-derived isothiocyanates and indole-3-carbinol likely contribute to the potential health-promoting effects of cruciferous vegetables. *(More information)*
- Variations in the sequence of genes coding for Phase II detoxification enzymes, glutathione *S*-transferases (GSTs), may influence the potential health benefits of consuming cruciferous vegetables. *(More information)*
- A few observational studies have examined the link between cruciferous vegetable consumption and cardiovascular health, but the results have been largely inconsistent. *(More information)*
- High intakes of cruciferous vegetables have been associated with lower risk of bladder, breast, colorectal, endometrial, gastric, lung, ovarian, pancreatic, prostate, and renal cancer. However, evidence of associations remains largely limited to case-control studies. *(More information)*
- The Dietary Guidelines for Americans recommend for adults to consume 1½-2½ cup-equivalents of dark-green vegetables per week, including cruciferous vegetables, as part of healthy meals. *(More information)*

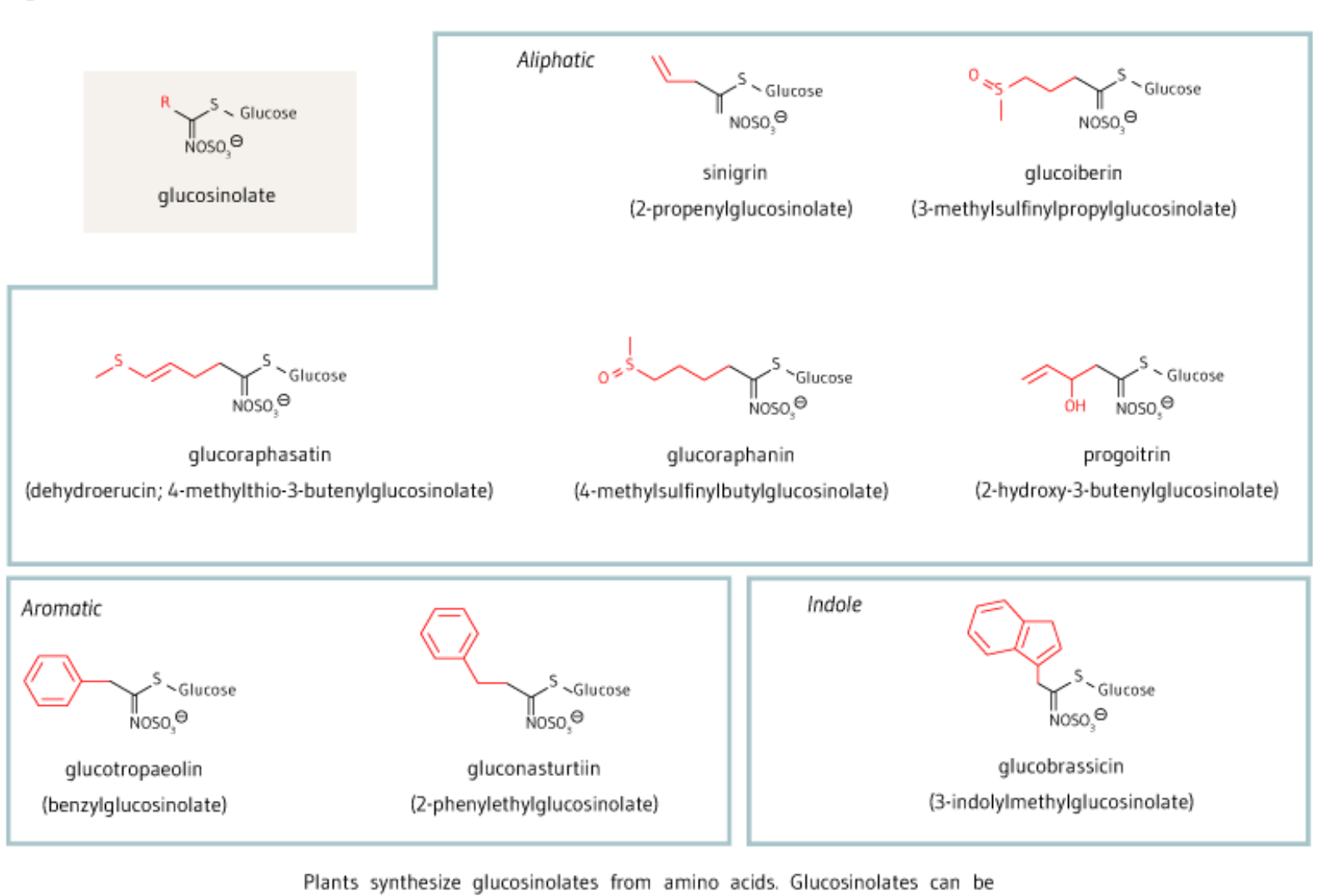
Introduction

Cruciferous or *Brassica* vegetables come from plants in the family known to botanists and biologists as Cruciferae or alternately, Brassicaceae. The Brassicaceae family, which includes the model plant *Arabidopsis thaliana*, comprises approximately 375 genera and over 3,000 species (1). Many, but not all, commonly consumed cruciferous vegetables come from the *Brassica* genus; examples include broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnips, bok choy, and Chinese cabbage (2). Examples of other edible crucifers include radish (*Raphanus sativus*), horseradish (*Armoracia rusticana*), watercress (*Nasturtium officinale*), and wasabi (*Wasabia japonica*) (2).

Cruciferous vegetables are unique in that they are a rich source of sulfur-containing compounds called glucosinolates (β-thioglucoside N-hydroxysulfates) that impart a pungent aroma and spicy (some say bitter) taste (**Figure 1**). Glucosinolates can be classified into three categories based on the chemical structure of their amino acid precursors: aliphatic glucosinolates (e.g., glucoraphanin), indole glucosinolates (e.g., glucobrassicin), and aromatic glucosinolates (e.g., gluconasturtiin) (**Figure 1**) (1). Around 130 glucosinolate structures have been described to date (3), but only a subset can be found in the human diet. In a cohort of 2,121 German participants in the European Prospective Investigation into Cancer and Nutrition (EPIC study), glucobrassicin, sinigrin, glucoraphasatin (dehydroerucin), glucoraphanin, and glucoiberin were found to contribute most to total glucosinolate intake (4).

Glucosinolates and their breakdown derivatives (metabolites), especially isothiocyanates and indole-3-carbinol, exert a variety of biological activities that may be relevant to health promotion and disease prevention in humans (see the MIC articles on Indole-3-Carbinol and Isothiocyanates).

Figure 1. Chemical Structures of Some Glucosinolates


Aliphatic
Aromatic
Indole
R
S
Glucose
NOSO$_3^-$
glucosinolate
sinigrin
(2-propenylglucosinolate)
glucoiberin
(3-methylsulfinylpropylglucosinolate)
glucoraphasatin
(dehydroerucin; 4-methylthio-3-butenylglucosinolate)
glucoraphanin
(4-methylsulfinylbutylglucosinolate)
progoitrin
(2-hydroxy-3-butenylglucosinolate)
OH
glucotropaeolin
(benzylglucosinolate)
gluconasturtiin
(2-phenylethylglucosinolate)
glucobrassicin
(3-indolylmethylglucosinolate)

Plants synthesize glucosinolates from amino acids. Glucosinolates can be classified based on their amino acid precursors. Aliphatic glucosinolates are derived from alanine, leucine, isoleucine, valine, and methionine. Aromatic glucosinolates are derived from phenylalanine or tyrosine, and tryptophan is the precursor of indole glucosinolates (Ishida, 2014).

[Figure 1 - Click to Enlarge]

Metabolism and Bioavailability of Glucosinolates

Metabolism

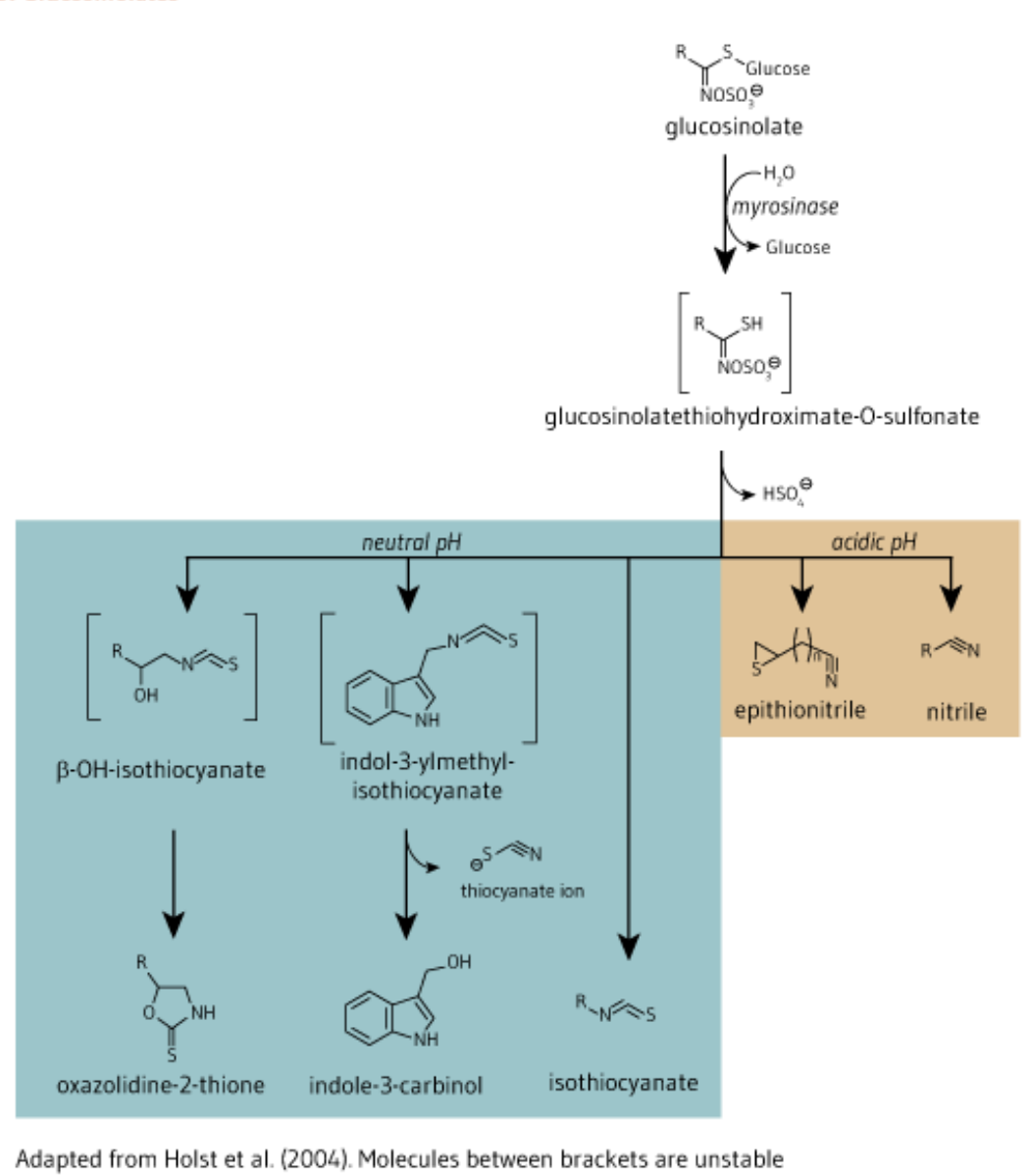
The hydrolysis of glucosinolates, which is catalyzed by a class of enzymes called myrosinases (β-thioglucosidases), leads to the formation of breakdown compounds, such as thiocyanates, isothiocyanates, indoles, oxazolidine-2-thiones (e.g., goitrin), epithionitrile, and nitrile (**Figure 2**). In intact plant cells, myrosinase is physically separated from glucosinolates. Yet, when plant cells are damaged, myrosinase is released and comes in contact with glucosinolates, catalyzing their conversion into highly reactive metabolites. In plants, thiocyanates, isothiocyanates, epithionitrile, and nitrile are defensive compounds against pathogens, insects, and herbivores (1). When raw cruciferous vegetables are chopped during the cooking process, glucosinolates are rapidly hydrolyzed by myrosinase, generating metabolites that are then absorbed in the proximal intestine. In contrast, boiling cruciferous vegetables before consumption inactivates myrosinase, thus preventing the breakdown of glucosinolates. A small fraction of intact glucosinolates may be absorbed in the small intestine, but a large proportion reaches the colon (5). Of note, boiling cruciferous vegetables has also been found to reduce their glucosinolate content to a much greater extent than steam cooking, microwaving, and stir-frying do (5). Nonetheless, when cruciferous vegetables are cooked, bacterial myrosinase-like activity in the colon is mainly responsible for glucosinolate degradation, generating a wide range of metabolites (5, 6).

A neutral pH may favor the formation of isothiocyanates from glucosinolates (**Figure 2**). Once absorbed, isothiocyanates, such as glucoraphanin-derived sulforaphane, are conjugated to glutathione in the liver, and then sequentially metabolized in the mercapturic acid pathway (**Figure 3**). Sulforaphane metabolites — sulforaphane-glutathione, sulforaphane-glycine, sulforaphane-cysteine, and sulforaphane N-acetylcysteine (**Figure 3**) — collectively known as dithiocarbamates, are ultimately excreted in the urine (5).

Bioavailability

The composition and content of glucosinolates in cruciferous vegetables are relatively stable, yet depend on the genus and species and can vary with plant growing and post-harvest storage conditions and culinary processing (7, 8). Since most cruciferous vegetables are cooked prior to eating, bacterial myrosinase-like activity in the gut rather than plant myrosinase is responsible for the initial step in glucosinolate degradation (**Figure 2**). In a feeding study involving 45 healthy subjects, the mean conversion rate of glucosinolates (of which 85% was glucoraphanin) to dithiocarbamates over a 24-hour period was estimated to be around 12% with wide variations among participants (range, 1.1 to 40.7%) (7). In contrast, 70%-75% of ingested isothiocyanates were found to be metabolized to dithiocarbamates. Therefore, following the ingestion of cooked cruciferous vegetables, the conversion of glucosinolates into isothiocyanates by gut bacteria appears to be a limiting step in the generation of dithiocarbamates (7). However, differences in individuals' capacity to metabolize glucosinolates have not been linked to differences in gut microbiota composition (9).

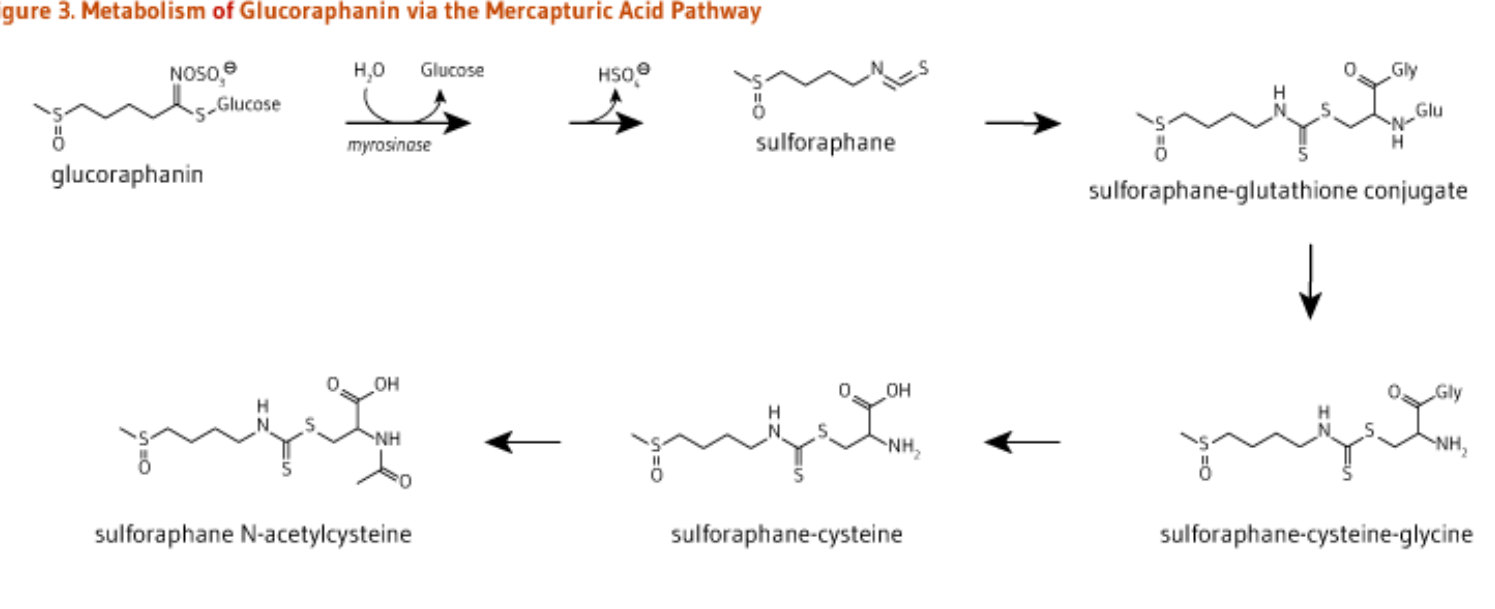
Figure 2. Breakdown of Glucosinolates



Adapted from Holst et al. (2004). Molecules between brackets are unstable intermediates.

[Figure 2 - Click to Enlarge]

Figure 3. Metabolism of Glucoraphanin via the Mercapturic Acid Pathway


glucoraphanin
H2O
Glucose
myrosinase
HSO4
sulforaphane
sulforaphane-glutathione conjugate
sulforaphane-cysteine-glycine
sulforaphane-cysteine
sulforaphane N-acetylcysteine

[Figure 3 - Click to Enlarge]

Disease Prevention

Like most other vegetables, cruciferous vegetables are good sources of a variety of nutrients and phytochemicals that synergistically contribute to health promotion (see Bioactive compounds in cruciferous vegetables) (10). One challenge in studying the relationships between cruciferous vegetable intake and disease risk in humans is dissociating the benefits of whole diets that are generally rich in vegetables from those that are specifically rich in cruciferous vegetables (11). One characteristic that sets cruciferous vegetables apart from other vegetables is their high glucosinolate content (see Introduction). Glucosinolate hydrolysis products may play important roles in disease prevention by triggering antioxidant and anti-inflammatory response and contributing to the maintenance of cell homeostasis (see the MIC articles on Isothiocyanates and Indole-3-Carbinol).

Genetic influences

Once absorbed, glucosinolate-derived isothiocyanates (like sulforaphane) are promptly conjugated to glutathione by a class of phase II detoxification enzymes known as glutathione *S*-transferases (GSTs) (**Figure 3**). This mechanism is meant to increase the solubility of isothiocyanates, thereby promoting a rapid excretion in the urine. Isothiocyanates are thought to play a prominent role in the potential anticancer and cardiovascular benefits associated with cruciferous vegetable consumption (12, 13). Genetic variations in the sequence of genes coding for GSTs may affect the activity of these enzymes. Such variations have been identified in humans. Specifically, null variants of the *GSTM1* and *GSTT1* alleles contain large deletions, and individuals who inherit two copies of the *GSTM1*-null or *GSTT1*-null alleles cannot produce the corresponding GST enzymes (14). It has been proposed that a reduced GST activity in these individuals would slow the rate of excretion of isothiocyanates, thereby increasing tissue exposure to isothiocyanates after cruciferous vegetable consumption (15). However, human interventional studies with watercress report there is no difference in the isothiocyanate excretion rate between positive ($^{+/+}$) and null ($^{-/-}$) genotypes (16). Similar studies with broccoli have shown that *GSTM1*$^{-/-}$ individuals excreted a greater proportion of ingested sulforaphane via mercapturic acid metabolism than *GSTM1*$^{+/+}$ individuals (17, 18). In addition, GSTs are involved in "detoxifying" potentially harmful substances like carcinogens, suggesting that individuals with reduced GST activity might also be more susceptible to cancer (19-21). Finally, induction of the expression and activity of GSTs and other phase II detoxification/antioxidant enzymes by isothiocyanates is an important defense mechanism against oxidative stress and damage associated with the development of diseases like cancer and cardiovascular disease (22). The ability of sulforaphane (glucoraphanin-derived isothiocyanate) to reduce oxidative stress in different settings is linked to activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway. Yet, whether potential protection conferred by isothiocyanates via the Nrf2-dependent pathway is diminished in individuals carrying *GST*$^{-/-}$ variants is currently unknown.

Some, but not all, observational studies have found that GST genotypes could influence the associations between isothiocyanate intake from cruciferous vegetables and risk of disease (23).

Cardiovascular disease

High intakes of fruit and vegetables have been consistently associated with a reduced risk of cardiovascular disease (CVD) (24, 25). Yet, few observational studies have specifically examined the potential benefits of cruciferous vegetable consumption. In the Shanghai Women's Health Study (mean follow-up, 10.2 years) and the Shanghai Men's Health Study (mean follow-up, 4.6 years), which included a total of 134,796 Chinese adults, participants in the highest versus lowest quintile of cruciferous vegetable intakes had a 22% reduced risk of all cause-mortality and a 31% reduced risk of CVD-related mortality (26). In contrast, a pooled analysis of two large US prospective cohort studies, the Nurses' Health Study (70,870 women) and the Health Professionals' Follow-Up Study (38,918 men), found no significant association between cruciferous vegetable intake and combined risk of myocardial infarction (MI) and ischemic stroke (27). A case-control study conducted in 2,042 subjects (ages, <75 years) who survived a first acute myocardial infarction (MI), and matched healthy controls with no CVD history found that the individuals in the highest versus lowest tertile of cruciferous vegetable intakes (6 times/week versus <1 time/week) had 27% lower odds of MI (28). However, further analyses showed that the association between cruciferous vegetable intake and MI events was significant in individuals with two functional *GSTT1* alleles but not in carriers of two alleles of the *GSTT1* null variant ($^{-/-}$) (28).

Analysis of data from two 12-week randomized controlled trials in 130 participants with mild or moderate CVD risk found that the consumption of 400 g/week of high-glucosinolate broccoli (containing 3 to 6 times more glucoraphanin and glucoiberin than standard broccoli) resulted in a significant reduction in low-density lipoprotein (LDL)-cholesterol concentration in plasma compared with standard broccoli (29). Whether the effect of glucosinolates on cholesterol metabolism might be beneficial in the prevention of CVD needs further investigation.

Cancer

A recent intervention study demonstrated that cruciferous vegetables could increase the detoxification of carcinogens and other xenobiotics in humans. In this 12-week randomized controlled trial in 391 healthy Chinese adults exposed to high levels of air pollution, daily consumption of a broccoli sprout-rich beverage (providing 600 μmol/day of glucoraphanin and 40 μmol/day of sulforaphane) significantly increased the urinary excretion of a known carcinogen, benzene, and a toxicant, acrolein, compared to placebo (20). The biological activities of glucosinolate derivatives, isothiocyanates and indole-3-carbinol, which include modulation of xenobiotic metabolism, but also antioxidant and anti-inflammatory properties, induction of cell cycle arrest and apoptosis, and inhibition of angiogenesis, likely contribute to the potential benefits of cruciferous vegetables in the prevention of cancer (see the MIC articles on Isothiocyanates and Indole-3-Carbinol) (23).

Evidence from observational studies

Numerous observational studies have examined the relationship between cruciferous vegetable intake and cancer risk. Results from recent published meta-analyses of observational studies are reported in **Table 1** (adapted from 23).

Table 1. Cruciferous Vegetables and Cancer Risk: Meta-analyses of Observational Studies

Type of Cancer	Type of Observational Studies	Relative Risk [RR] or Odds Ratio [OR] (95% Confidence Interval)	Relative Risk [RR] in Subgroup Analyses (e.g., by food group or study type)	References
Bladder cancer	5 prospective cohort and 5 case-control studies	RR: 0.80 (0.69-0.92)	RR: 0.78 (0.67-0.89) with case-control studies only RR: 0.86 (0.61-1.11) with cohort studies only	Liu et al. (2013) (30)
	12 prospective cohort and case-control studies	RR: 0.84 (0.77-0.91)		Yao et al. (2014) (31)
	7 prospective cohort and case-control studies	RR: 0.85 (0.69-1.06)		Vieira et al. (2015) (32)
	8 prospective cohort studies	RR: 0.97 (0.93-1.01)		Xu et al. (2015) (33)
Breast cancer	11 case-control studies	RR: 0.85 (0.77-0.94)		Liu et al. (2013) (34)
Colorectal cancer	24 case-control and 11 prospective cohort studies	RR: 0.82 (0.75-0.90)	RR: 0.76 (0.60-0.97) for studies reporting on cabbage intake RR: 0.82 (0.65-1.02) for studies reporting on broccoli intake	Wu et al. (2013) (35)
	11 prospective cohort and 18 case-control studies	OR: 0.92 (0.83-1.01)	OR: 0.84 (0.72-0.98) for colon cancer OR: 0.99 (0.67-1.46) for rectal cancer OR: 1.09 (0.90-1.33) for colonic adenoma OR: 0.80 (0.65-0.99) for studies reporting on broccoli intake OR: 0.95 (0.80-1.14) for studies reporting on cabbage intake OR: 1.0 (0.75-1.34) for studies reporting on Brussels sprouts	Tse et al. (2014) (36)
Endometrial cancer	1 prospective cohort study and 16 case-control studies	OR: 0.79 (0.69-0.90) per 100 g/day		Bandera et al. (2007) (37)
Gastric cancer	6 prospective cohort and 16 case-control studies	RR: 0.81 (0.75-0.88)	RR: 0.78 (0.71-0.86) for case-control studies RR: 0.89 (0.77-1.02) for cohort studies RR: 0.68 (0.58-0.80) for studies reporting on cabbage intake	Wu et al. (2013) (38)
Lung cancer	6 prospective cohort and 13 case-control studies		RR: 0.77 (0.68-0.88) for case-control studies RR: 0.83 (0.62-1.08) for cohort studies	Lam et al. (2009) (39)
	5 prospective cohort and 6 case-control studies	RR: 0.75 (0.63-0.89)		Wu et al. (2013) (40)
Ovarian cancer	5 prospective cohort and 6 case-control studies	RR: 0.90 (0.82-0.98)	RR: 0.84 (0.75-0.94) for case-control studies RR: 1.0 (0.85-1.11) for cohort studies	Han et al. (2014) (41)
	4 prospective cohort and 4 case-control studies	RR: 0.89 (0.81-0.99)		Hu et al. (2015) (42)
Pancreatic cancer	4 prospective cohort and 5 case-control studies	OR: 0.79 (0.64-0.91)	OR: 0.72 (0.55-0.89) for case-control studies OR: 0.87 (0.67-1.06) for cohort studies OR: 0.78 (0.55-1.01) for high-quality studies OR: 0.80 (0.66-0.94) for low-quality studies	Li et al. (2015) (43)
Prostate cancer	7 prospective cohort and 6 case-control studies	RR: 0.90 (0.85-0.96)	RR: 0.79 (0.69-0.89) for case-control studies RR: 0.95 (0.89-1.02) for cohort studies	Liu et al. (2012) (44)
Renal cell carcinoma	6 prospective cohort and 6 case-control studies	RR: 0.81 (0.72-0.91)	RR: 0.89 (0.82-0.98) for high-quality studies RR: 0.72 (0.64-0.81) for case-control studies RR: 0.92 (0.84-1.00) for cohort studies	Zhao et al. (2013) (45)
	3 prospective cohort and 7 case-control studies	RR: 0.73 (0.63-0.83)	RR: 0.69 (0.60-0.78) for case-control studies RR: 0.96 (0.71-1.21) for cohort studies	Liu et al. (2013) (46)

Most meta-analyses found inverse associations between cruciferous vegetable intake and risk of bladder, breast, colorectal, endometrial, gastric, lung, ovarian, pancreatic, prostate, and renal cancer. Subgroup analyses showed that inverse associations remained significant in pooled analyses of case-control studies but not in pooled analyses of prospective cohort studies (see **Table 1**). Retrospective case-control studies are susceptible to bias in the selection of participants (cases and controls) and prone to dietary recall bias compared to prospective cohort studies, which collect dietary information from participants before they are diagnosed with cancer (47). The method of cooking cruciferous vegetables, which strongly affects the bioavailability and potential anticancer benefits of isothiocyanates (see Metabolism and Bioavailability of Glucosinolates) may be a source of bias and explain variation in the results of the studies (heterogeneity among studies). The lack of information regarding cooking methods prevented data adjustment to reduce bias.

In the past decades, some observational studies have examined the effect of individuals' genetic variations on the relationship between cruciferous vegetable intake and the risk of different cancer types. For example, a pooled analysis of two prospective cohort studies and six case-control studies found an inverse association between cruciferous vegetable consumption and risk of colorectal neoplasm in carriers of the *GSTT1* null variant but not in individuals with the *GSTM1* null variant or those with both the *GSTT1*and *GSTM1* null variants ($^{-/-}$) (36). The results of a pooled analysis of five case-control studies also suggested a stronger association between cruciferous vegetable intake and lung cancer in carriers of both the *GSTT1*$^{-/-}$ and *GSTM1*$^{-/-}$ variants compared to carriers of wild-type alleles ($^{+/+}$); however, it was not reported whether results from these two groups of individuals were significantly different (39). There is also a significant body of evidence suggesting that *GSTM1*$^{+/+}$ individuals gain greater cancer protection from consumption total cruciferous vegetables or broccoli compared to *GSTM1*$^{-/-}$ variant carriers (25, 48, 49). Current evidence is scarce, and adequately powered, well-designed studies are required to assess and explain potential interactions between cruciferous vegetable intake and GST genotypes.

A few observational studies have looked at whether cruciferous vegetable intake could be associated with reduced risks of disease progression and mortality. The highest versus lowest intake of cruciferous vegetables (assessed before diagnosis) was associated with a better survival rate over 72 months after diagnosis in 547 women with lung cancer (50). A prospective study in 29,361 men who underwent a prostate-specific antigen (PSA) test found that intake of cruciferous vegetables was inversely associated with risk of metastatic prostate cancer — cancer that has spread beyond the prostate (i.e., late-stage prostate cancer) — during a mean follow-up of 4.2 years (51). Another prospective study in 1,560 men diagnosed with non-metastatic prostate cancer reported that higher post-diagnosis intake of cruciferous vegetables was associated with a 59% lower risk of prostate cancer progression during a two-year period after completion of the dietary assessment (52). In contrast, cruciferous vegetable consumption in a cohort of 11,390 women with stage I-III invasive breast cancer (from four US and Chinese prospective studies), assessed about two years after diagnosis, was not found to be associated with risk of cancer recurrence or total mortality (53).

Nutrient Interactions

Iodine and thyroid function

Very high intakes of cruciferous vegetables, such as cabbage and turnips, have been found to cause hypothyroidism (insufficient production of thyroid hormones) in animals (54). Two mechanisms can potentially explain this effect. The hydrolysis of progoitrin, found in cruciferous vegetables (see **Figure 1**), may yield a compound known as goitrin, which may interfere with thyroid hormone synthesis. The hydrolysis of another class of glucosinolates, known as indole glucosinolates, results in the release of thiocyanate ions (see **Figure 2**) that can compete with iodine for uptake by the thyroid gland (55). However, increased exposure to thiocyanate ions from cruciferous vegetable consumption or, more commonly, from cigarette smoking, does not appear to increase the risk of hypothyroidism unless accompanied by iodine deficiency. One study in humans found that the consumption of 150 g/day (5 oz/day) of cooked Brussels sprouts for four weeks had no adverse effects on thyroid function (56). Similarly, consumption of high amounts of cruciferous vegetables has been associated with increased thyroid cancer risk only in iodine-deficient areas (57).

Intake Recommendations

The 2015-2020 Dietary Guidelines for Americans recommend eating a variety of vegetables daily (2½ cup-equivalents/day for a 2,000 calorie diet) from all of the five vegetable subgroups (dark green, red and orange, legumes, starchy, and other; see 58). No separate recommendations have been established for cruciferous vegetables, yet the 2015-2020 Dietary Guidelines for Americans recommend that adults consume 1½-2½ cup-equivalents of dark-green vegetables (which include cruciferous vegetables) per week (58).

Bioactive compounds in cruciferous vegetables

Cruciferous vegetables are important sources of some vitamins and minerals, fiber, and various phytochemicals other than glucosinolates (**Table 2**). Many of these compounds likely contribute to the potential health-promoting benefits of cruciferous vegetables.

Table 2. Some Potentially Beneficial Compounds in Cruciferous (*Brassica*) Vegetables

Vitamins	Minerals	Phytochemicals
Folate	Potassium	Carotenoids
Vitamin C	Selenium	Chlorophyll
Vitamin K	Calcium	Fiber
		Flavonoids
		Indole-3-Carbinol
		Isothiocyanates
		Lignans
		Phytosterols
		Sulfur bioactives (other than glucosinolates) (59)

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Garlic

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Garlic and Organosulfur Compounds

日本語

Summary

- Garlic (*Allium sativum* L.) is a particularly rich source of organosulfur compounds, which are currently under investigation for their potential to prevent and treat disease. *(More information)*
- The two main classes of organosulfur compounds found in whole garlic cloves are L-cysteine sulfoxides and γ-glutamyl-L-cysteine peptides. *(More information)*
- Crushing or chopping garlic releases an enzyme called alliinase that catalyzes the formation of allicin from S-allyl-L-cysteine sulfoxide (Allin). Allicin rapidly breaks down to form a variety of organosulfur compounds. *(More information)*
- *In vivo* studies indicate that allicin-derived organosulfur compounds may be poorly bioavailable, whereas water-soluble derivatives of γ-glutamyl-L-cysteine peptides have been detected in plasma, liver, and kidney following oral consumption. *(More information)*
- Several different types of garlic supplements are available commercially, and each type provides a different profile of organosulfur compounds depending on how it was processed. *(More information)*
- Numerous preclinical studies reported that organosulfur compounds from garlic could exert antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective activities in various experimental settings. *(More information)*
- The results of randomized controlled trials suggested that garlic supplementation modestly improves serum lipid profiles in individuals with elevated serum cholesterol and reduces blood pressure in hypertensive subjects, at least in the short term. It is not known whether garlic supplementation can help prevent cardiovascular disease. *(More information)*
- Current evidence from observational studies does not support an association between high intakes of garlic and prevention of cancer, including gastric and colorectal cancer. It is not known whether garlic-derived organosulfur compounds may be effective in preventing or treating human cancers. *(More information)*

Introduction

Garlic (*Allium sativum* L.) has been used for culinary and medicinal purposes in many cultures for centuries (1). Garlic is a particularly rich source of organosulfur compounds, which are thought to be responsible for its flavor and aroma, as well as its potential health benefits (2). Consumer interest in the health benefits of garlic is strong enough to place it among the best-selling herbal supplements in the United States (3). Scientists are interested in the potential for organosulfur compounds derived from garlic to prevent and treat chronic diseases, such as cancer and cardiovascular disease (4).

Organosulfur compounds from garlic

Two classes of organosulfur compounds are found in whole garlic cloves: L-cysteine sulfoxides and γ-glutamyl-L-cysteine peptides.

L-Cysteine sulfoxides

S-allyl-L-cysteine sulfoxide (alliin) accounts for approximately 80% of cysteine sulfoxides in garlic (**Figure 1**) (5). When raw garlic cloves are crushed, chopped, or chewed, an enzyme known as alliinase is released. Alliinase catalyzes the formation of sulfenic acids from L-cysteine sulfoxides (**Figure 2**). Sulfenic acids spontaneously react with each other to form unstable compounds called thiosulfinates. In the case of alliin, the resulting sulfenic acids react with each other to form a thiosulfinate known as allicin (half-life in crushed garlic at 23°C is 2.5 days). The formation of thiosulfinates is very rapid and has been found to be complete within 10 to 60 seconds of crushing garlic. Allicin breaks down *in vitro* to form a variety of fat-soluble organosulfur compounds (**Figure 2**), including diallyl trisulfide (DATS), diallyl disulfide (DADS), and diallyl sulfide (DAS), or in the presence of oil or organic solvents, ajoene and vinyldithiins (6). *In vivo*, allicin can react with glutathione and L-cysteine to produce S-allylmercaptoglutathione (SAMG) and S-allylmercaptocysteine (SAMC), respectively (**Figure 2**) (4).

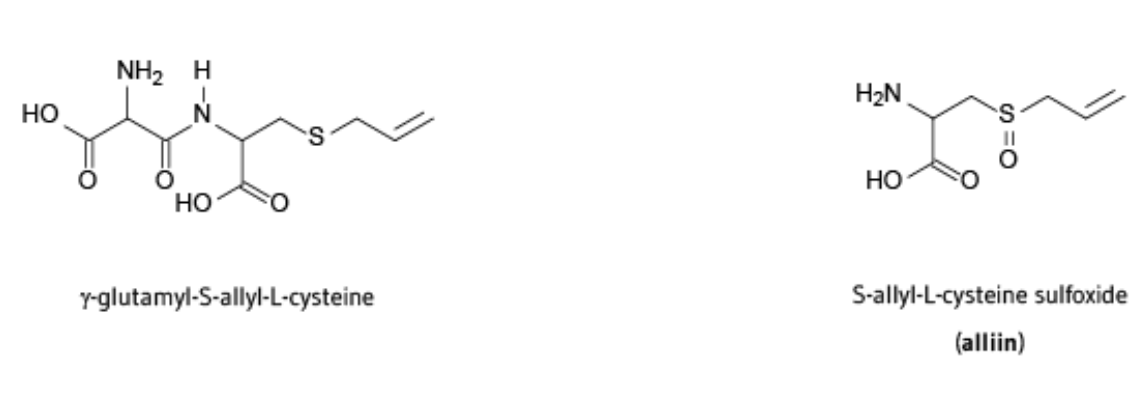
γ-Glutamyl-L-cysteine peptides

Crushing garlic does not change its γ-glutamyl-L-cysteine peptide content. γ-Glutamyl-L-cysteine peptides include an array of water-soluble dipeptides, including γ-glutamyl-S-allyl-L-cysteine, γ-glutamylmethylcysteine, and γ-glutamylpropylcysteine (see **Figure 1**). Water-soluble organosulfur compounds, such as S-allylcysteine and SAMC (**Figure 3**), are formed from γ-glutamyl-S-allyl-L-cysteine during long-term incubation of crushed garlic in aqueous solutions, as in the manufacture of aged garlic extracts (see Sources).

Non-sulfur garlic phytochemicals

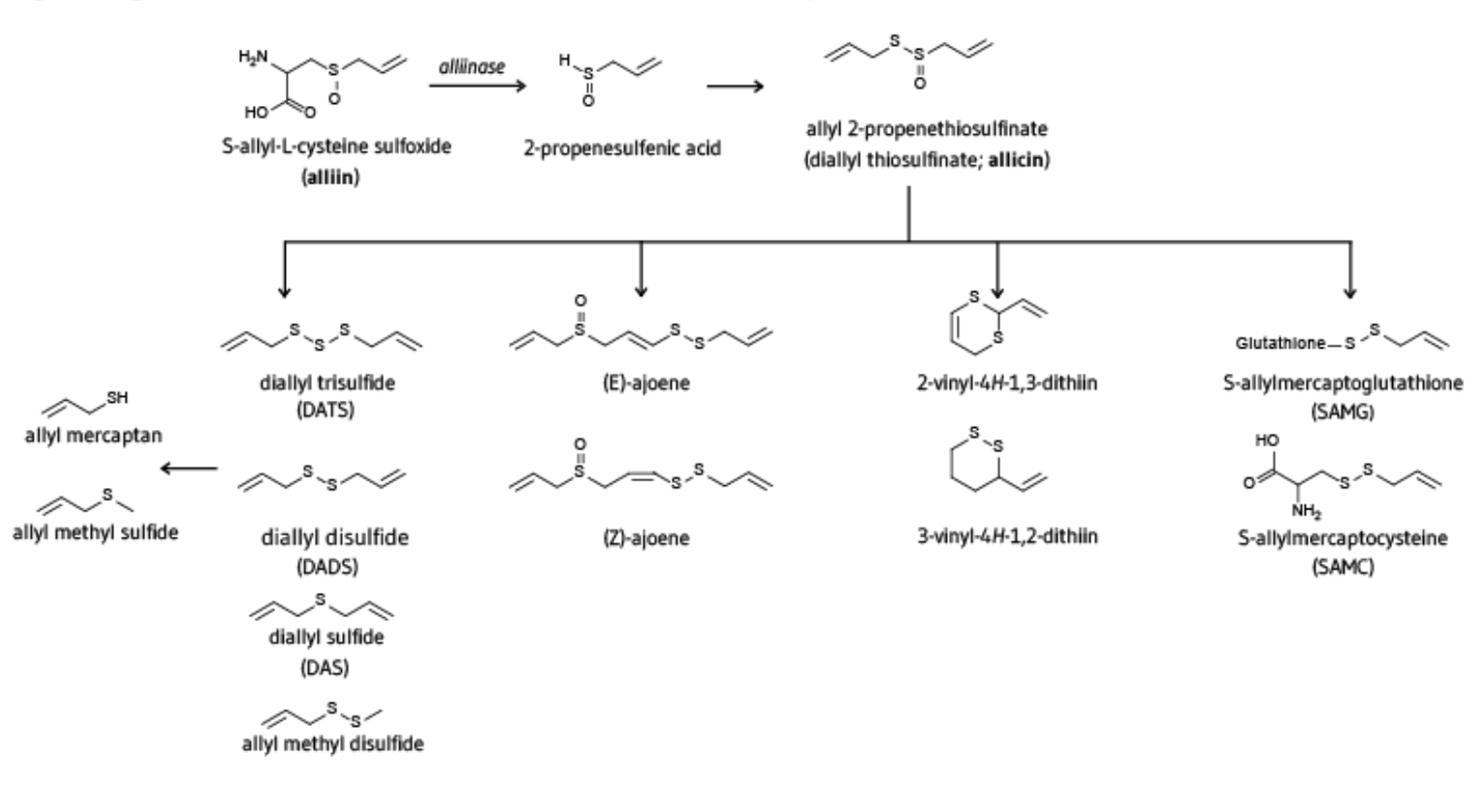
Although little is known about their bioavailability and biological activities, non-sulfur garlic phytochemicals, including flavonoids, steroid saponins, organoselenium compounds, and allixin, likely work in synergy with organosulfur compounds (6).

Figure 1. Major Nonvolatile Sulfur-containing Compounds in Intact Garlic



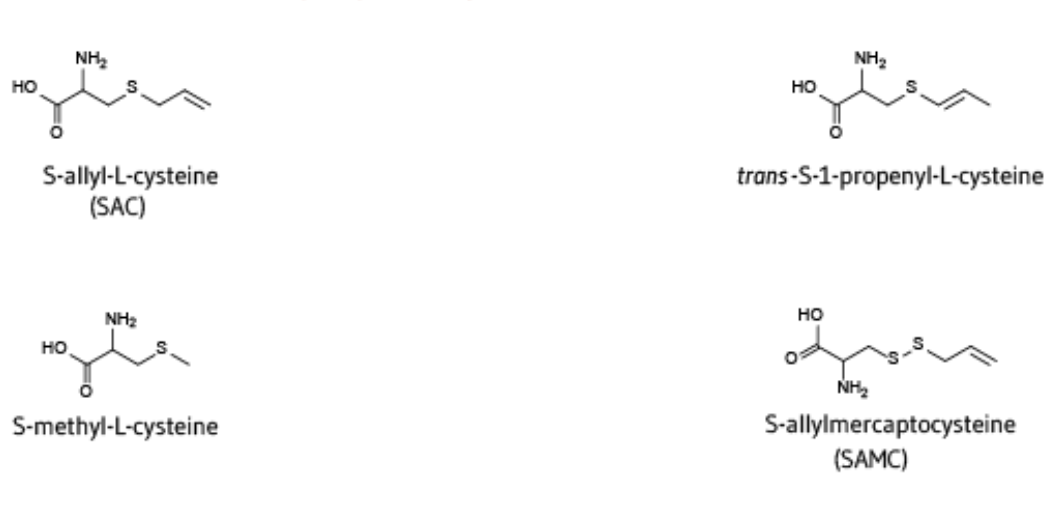
[Figure 1 - Click to Enlarge]

Figure 2. Organosulfur Derivatives of Alliin in the Process of Garlic Product Preparation



[Figure 2 - Click to Enlarge]

Figure 3. Major Water-soluble Derivatives of γ-Glutamyl-L-cysteine Peptides



[Figure 3 - Click to Enlarge]

Metabolism and Bioavailability

S-Allyl-L-cysteine sulfoxide (Alliin)

In studies conducted in rodents, orally administrated alliin was found to be absorbed intact and to reach plasma and liver without being converted to allicin. There are no thiosulfinates (like allicin) in intact garlic cloves, and none can be generated in the stomach because alliinase would be irreversibly inhibited under acidic conditions (6).

Allicin and derivatives

The absorption and metabolism of allicin and allicin-derived compounds (see **Figure 2**) are only partially understood (7). In humans, no allicin has been detected in the serum or urine up to 24 hours after the ingestion of 25 g of raw garlic containing a significant amount of allicin (8). Before ingestion in garlic preparations and after ingestion in the stomach, allicin likely breaks down to release a number of volatile compounds, including DAS and DADS. These organosulfur compounds are metabolized to allyl mercaptan, allyl methyl sulfide, and allyl methyl disulfide, which have been detected in human breath after garlic consumption (9-11). Although a number of biological activities have been attributed to various allicin-derived compounds, it is not yet clear which of these compounds or metabolites actually reaches target tissues (5). Allyl methyl sulfide — but not allyl mercaptan — has been detected in the urine within four hours of garlic ingestion, suggesting that this compound is absorbed into the circulation and rapidly excreted (11). Other allicin-derived compounds, including diallyl sulfides, ajoenes, and vinyldithiins, have not been detected in human blood, urine, or stool, even after the consumption of up to 25 g of fresh garlic or 60 mg of pure allicin (5). These findings suggest that, if they are absorbed, allicin and allicin-derived compounds are rapidly metabolized.

γ-Glutamyl-S-allyl-L-cysteine and derivatives

γ-Glutamyl-S-allyl-L-cysteine is thought to be absorbed intact and hydrolyzed to S-allyl-L-cysteine (SAC) and *trans*-S-1-propenyl-L-cysteine (see **Figure 3**), since metabolites of these compounds have been measured in human urine after garlic consumption (12, 13). The consumption of aged garlic extract, a commercial garlic preparation that contains SAC, has been found to increase plasma SAC concentrations in humans (14-16). SAC has been detected in plasma, liver, and kidney of SAC-fed animals (17). Water-soluble organosulfur compounds like SAC and its metabolite, N-acetyl-S-allyl-L-cysteine, may be used as reliable markers of compliance in clinical trials involving garlic intake (6, 18).

Biological Activities

Antioxidant activity

Glutathione

Low cellular concentrations of glutathione, a major intracellular antioxidant, and/or overproduction of reactive oxygen species (ROS) can lead to oxidative stress-induced damage to biological macromolecules and contribute to the development and progression of pathological conditions. In endothelial cells (that line the inner wall of blood vessels), garlic-derived allicin lowered ROS production and increased the concentration of glutathione (19). Oral administration of allicin to mice lowered ROS production and prevented ROS-induced cardiac hypertrophy by inhibiting pro-inflammatory pathways like mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase 3β (GSK3β) signaling pathways (20). It is thought that, upon crossing cell membranes, allicin interacts with glutathione and forms SAMG (see **Figure 2**), which could prolong the antioxidant activity of allicin (19).

Nrf2-dependent antioxidant pathway

Allicin was also found to upregulate the expression of glutamate-cysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis, and other Phase II detoxifying/antioxidant enzymes, likely via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway (19). Briefly, Nrf2 is a transcription factor that is bound to the protein Kelch-like ECH-associated protein 1 (Keap1) in the cytosol. Keap1 responds to oxidative stress signals by freeing Nrf2. Upon release, Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE) located in the promoter of genes coding for antioxidant/detoxifying enzymes and scavengers. Nrf2/ARE-dependent genes code for numerous mediators of the antioxidant response, including GCL, glutathione S-transferases (GSTs), thioredoxin, NAD(P)H quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) (21). Like allicin, oil-soluble organosulfides, DADS and DATS (see **Figure 2**), have been shown to stimulate Nrf2-dependent antioxidant pathway (4). For example, antioxidant and cytoprotective effects of DADS against acute ethanol-induced liver damage in mice were associated with the ability to trigger Nrf2-dependent HO-1 activation (22). DATS protected cardiac cells *in vitro* and in experimental diabetic rats from high glucose-induced oxidative stress and apoptosis by inducing PI3K/Akt-dependent Nrf2 antioxidant signaling (23).

Aged garlic extract have also been shown to increase expression of antioxidant enzymes via the Nrf2/ARE pathway (24). SAC, a major organosulfur compound in aged garlic extract, prevented renal damage caused by ROS in cisplatin-treated rats, by limiting cisplatin-induced reduction of glutathione level, Nrf2 expression, and activity of several antioxidant enzymes (catalase, glutathione reductase, glutathione peroxidase) (25). SAC also protected neurons from oxidative damage and apoptosis in wild-type mice but not in mice without a functional Nrf2 signaling pathway (26).

Nitric oxide (NO) signaling cascade

The generation of nitric oxide (NO) catalyzed by endothelial nitric oxide synthase (eNOS) plays a critical role in protecting the vascular endothelium from oxidative and inflammatory insults (27). ROS-induced NO inactivation can impair vascular endothelial function, contributing to various pathologies like atherosclerosis, hypertension, cardiovascular disease, and central nervous system disorders (27, 28). Interestingly, ingestion of 2 g of fresh garlic was found to increase NO plasma concentrations within two to four hours in healthy volunteers (29). DADS and DATS protected eNOS activity and NO bioavailability in cultured endothelial cells challenged with oxidized low-density lipoprotein (LDL) (30). In a model of traumatic brain injury in rats, allicin attenuated brain edema, neurological deficits, and apoptotic neuronal death, and exhibited antioxidant and anti-inflammatory effects, partly by increasing Akt-mediated eNOS activation (31). Aged garlic extract and SAC were also found to stimulate NO production in different experimental settings (32). In a model of erectile dysfunction in diabetic rats, SAC restored electrically-induced penile erection by stimulating eNOS activity and inhibiting the expression of NADPH oxidase (Nox) responsible for ROS overproduction (33).

Anti-inflammatory activity

Garlic-derived organosulfur compounds have been found to inhibit mediators of the inflammatory response, including cytokines, chemokines, adhesion molecules, and enzymes like cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) (34-36). Nuclear factor-kappa B (NF-κB) is a transcription factor that binds DNA and induces the transcription of the *COX-2* gene, other pro-inflammatory genes, as well as genes involved in cell proliferation, adhesion, survival, and differentiation. The anti-inflammatory effects of organosulfur compounds result from their ability to counteract the activation of pro-inflammatory pathways — like NF-κB-, MAPK-, and PI3K/Akt-dependent signaling pathways — by pro-inflammatory stimuli (4). DATS inhibited bacterial lipopolysaccharide (LPS)-induced macrophage activation by limiting LPS binding to toll-like receptor 4 (TLR4) and blocking the upregulation of TLR4 and TLR4-associated molecule MyoD88 expression (37). DATS also inhibited LPS-induced NF-κB-dependent expression of COX-2, iNOS, tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) (37). In a mouse model of inflammation, the decrease of LPS-induced paw edema by DATS was associated with reduced serum concentrations of the pro-inflammatory cytokines, TNF-α, IL-6, and monocyte chemotactic protein-1 (MCP-1) (36).

Protection of the cardiovascular system

Inhibition of cholesterol synthesis

Garlic and garlic-derived organosulfur compounds have been found to decrease the synthesis of cholesterol by hepatocytes (38). Several garlic-derived organosulfur compounds, including S-allylcysteine and ajoene, have been found to inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), a critical enzyme in the cholesterol biosynthesis pathway (39, 40). Garlic-derived compounds may also inhibit other enzymes in this pathway, including sterol 4α-methyl oxidase (41).

Inhibition of platelet aggregation

An increase in the ability of platelets to aggregate has been linked to the narrowing of blood vessels and the occurrence of acute thrombotic events. A variety of garlic-derived organosulfur compounds have been found to inhibit platelet aggregation in the test tube (42-44). Aged garlic extract was found to inhibit chemically stimulated platelet aggregation by downregulating the fibrinogen binding activity of glycoprotein IIb/IIIa fibrinogen receptor found on platelets (45, 46) and/or by preventing intraplatelet calcium mobilization (42).

Inhibition of vascular smooth muscle cell (VSMC) proliferation

The proliferation and migration of normally quiescent VSMCs are central features of vascular diseases, including atherosclerosis and coronary restenosis (when treated arteries become blocked again) (47). Although the significance of these findings for human cardiovascular disease is not yet clear, limited cell culture research suggested that organosulfur compounds from garlic could inhibit the proliferation and migration of VSMCs (39, 48, 49).

Inhibition of vascular cell adhesion molecules

An elevation of oxidized low-density lipoprotein (LDL) concentration in plasma has been involved in the pathogenesis of atherosclerosis. Oxidized LDL may stimulate the recruitment of inflammatory white blood cells from the blood to the arterial wall by inducing the expression of vascular cell adhesion molecules. DADS and DATS inhibited the expression of adhesion molecules, E-selectin and vascular cell adhesion molecule-1 (VCAM-1), on endothelial cell surface by reversing oxidized LDL-induced inhibition of PI3K/Akt and cAMP responsive element binding protein (CREB) signaling pathways (50).

Hydrogen sulfide-mediated vasodilatory activity

The preservation of normal arterial function plays an important role in cardiovascular disease prevention. Hydrogen sulfide (H_2S), a gaseous signaling molecule produced by some cells within the body, acts as a vasodilator (relaxes blood vessels) and thus may have cardioprotective properties (51, 52). H_2S production may be involved in vascular smooth muscle cell relaxation through regulating the opening/closing of potassium channels and/or enhancing NO-dependent signaling pathway (reviewed in 53). A study found that garlic-derived compounds are converted to hydrogen sulfide by red blood cells *in vitro* (54). However, human consumption of a high dose of raw garlic does not increase breath hydrogen sulfide levels, suggesting that significant metabolism of garlic compounds to hydrogen sulfide does not occur *in vivo* (11).

Note that the potential benefits of garlic consumption/supplementation on cardiovascular health may also be attributed to antioxidant and anti-inflammatory activities described above.

Anticancer activity

Effects on carcinogen metabolism

Inhibition of metabolic activation of carcinogens: Some chemical carcinogens do not become active carcinogens until they have been metabolized by Phase I biotransformation enzymes, such as those belonging to the cytochrome P450 (CYP) family. Inhibition of specific CYP enzymes involved in carcinogen activation inhibits the development of cancer in some animal models (55). In particular, DAS and its metabolites have been found to inhibit CYP2E1 activity *in vitro* (56, 57) and when administered orally at high doses to animals (58, 59). Oral administration of garlic oil and DAS to humans has also resulted in evidence of decreased CYP2E1 activity (60-62).

Induction of Phase II detoxifying enzymes: Reactions catalyzed by phase II detoxifying enzymes generally promote the elimination of drugs, toxins, and carcinogens from the body. Consequently, increasing the activity of phase II enzymes, such as glutathione S-transferases (GSTs) and NQO-1, may help prevent cancer by enhancing the elimination of potential carcinogens (see the Nrf2-dependent antioxidant pathway) (63). In animal studies, oral administration of garlic preparations and organosulfur compounds was found to increase the expression and activity of phase II enzymes in a variety of tissues (64-66). For example, DADS protected rodent liver against carbon tetrachloride (CCl_4; an environmental pollutant)-induced lipid peroxidation and cell necrosis by blocking CYP2E1-mediated CCL_4 metabolic activation and by upregulating Nrf2 downstream genes for NQO-1, HO-1, GCL, GST, and superoxide dismutase (SOD1) (67, 68).

Induction of cell cycle arrest

In normal cells, the cell cycle is tightly regulated to ensure faithful DNA replication and chromosomal segregation prior to cell division. When defects occur during DNA replication or chromosomal segregation and in case of DNA damage, the cell cycle can be transiently arrested at check points to allow for repair. Apoptosis is triggered when repair fails. Defective check points and evasion of apoptosis allow the unregulated division of cancer cells (69). Organosulfur compounds, including allicin, DAS, DADS, DATS, ajoene, and SAMC, have been found to induce cell cycle arrest when added to cancer cells in cell culture experiments (reviewed in 4, 70). DATS reduced the incidence of poorly differentiated prostate tumors and limited the number of metastatic lesions in the lungs of mice genetically modified to develop prostate adenocarcinomas (71). DATS was shown to inhibit cancer cell proliferation, as well as neuroendocrine differentiation — a hallmark of prostate cancer malignancy — but had no effect on apoptosis and markers of invasion (71). In a rat model of chemically induced colon cancer, inhibition of cell proliferation by aged garlic extract was associated with a reduction in the incidence of precancerous lesions and dysplastic adenomas, but not of adenocarcinomas (72).

Induction of apoptosis

Apoptosis is a physiological process of programmed death of cells that are genetically damaged or no longer necessary. Precancerous and cancerous cells are resistant to signals that induce apoptosis (73). Garlic-derived organosulfur compounds, including allicin, ajoene, DAS, DADS, DATS, and SAMC, have been found to induce apoptosis when added to various cancer cell lines grown in culture (reviewed in 4, 70). Oral administration of aqueous garlic extract and S-allylcysteine has been reported to enhance apoptosis in an animal model of oral cancer (74, 75). Garlic oil reduced the incidence of N-nitrosodiethylamine-induced liver nodules by preventing oxidative damage to lipids and DNA and by promoting apoptosis (76). Garlic oil upregulated the activity of various antioxidant enzymes and expression of pro-apoptotic effectors like Bax and Caspase-3 and downregulated the expression of the anti-apoptotic genes β-arrestin-2, Bcl-2, and Bcl-X (76).

Inhibition of angiogenesis

To fuel their rapid growth, invasive tumors must develop new blood vessels by a process known as angiogenesis. Anti-angiogenic properties of several organosulfur compounds, including alliin, DATS, and ajoene, have been observed in *in vitro* or *ex vivo* experiments (70). In human breast cancer cells, DADS inhibited TNF-α-induced release of MCP-1, a chemokine that promotes tissue remodeling, angiogenesis, and metastasis (77). Aged garlic extract was also found to suppress *in vitro* angiogenesis by inhibiting endothelial cell proliferation, loss of adhesion, motility, and tube formation (78).

Antimicrobial activity

Garlic extracts have been found to have antibacterial and antifungal properties (79, 80). Thiosulfinates, particularly allicin, are thought to play an important role in the antimicrobial activity of garlic (80-82). Allicin-derived compounds, including DATS and ajoene, also have some antimicrobial activity *in vitro* (5). To date, randomized controlled trials using oral garlic preparations have not provided strong evidence for such activity in humans (83-85). A small randomized controlled trial found that application of 1% ajoene cream to the skin twice daily was as effective in treating tinea pedis (fungal skin infection known as athlete's foot) as 1% terbinafine (Lamisil) cream (86). In another preliminary randomized controlled trial, circulating immune innate cells (γδT-lymphocytes and natural killer (NK) cells), isolated from healthy adults supplemented with aged garlic extract, proliferated better in *ex vivo* culture than those from volunteers who consumed a placebo, suggesting a greater pathogen-fighting ability. The number of self-reported illnesses was similar between groups after 90 days of aged garlic extract or placebo supplementation, but aged garlic extract significantly reduced the severity of self-reported cold or flu symptoms (87).

Disease Prevention

Cardiovascular disease

Interest in garlic and its potential to prevent cardiovascular disease began with observations that people living near the Mediterranean basin had lower mortality from cardiovascular disease (88). Garlic is a common ingredient in Mediterranean cuisine, but a number of characteristics of the "Mediterranean diet" have been proposed to explain its cardioprotective effects (89). Although few observational studies have examined associations between garlic consumption and cardiovascular disease risk, numerous intervention trials have explored the effects of garlic supplementation on cardiovascular disease risk factors.

Platelet aggregation

Platelet aggregation is one of the first steps in the formation of blood clots that can occlude coronary or cerebral arteries, leading to myocardial infarction or ischemic stroke, respectively. Evidence that garlic inhibits platelet aggregation is based mainly on *in vitro* experiments and a small number of *ex vivo* assays. Of 10 randomized controlled trials that tested the antithrombotic effect of garlic preparation, four reported a modest but significant decrease in *ex vivo* platelet aggregation with garlic supplementation compared to placebo (reviewed in 90). Because garlic oil extract in particular may have antithrombotic activity, a small randomized controlled trial in 12 healthy adults was conducted to test the acute effect of one large dose of garlic oil (extracted from 9.9 g of fresh garlic) on *ex vivo* platelet aggregation (91). The garlic oil extract had a mild effect on adrenaline-induced platelet aggregation (12% reduction) but had no effect on adenosine diphosphate (ADP)- or collagen-induced aggregation measured four hours post-consumption. Another study in 14 healthy volunteers showed that aged garlic extract dose-dependently inhibited ADP-stimulated platelet aggregation by downregulating the fibrinogen binding activity of glycoprotein IIb/IIIa fibrinogen receptor found on platelets (46).

Serum lipid profiles

A recent systematic review of randomized controlled trials examining the effect of supplementation with various garlic preparations on serum lipid profiles in individuals with elevated and normal serum cholesterol levels reported mixed results (92). The most recent and comprehensive meta-analysis compared the results from 39 randomized controlled trials published between 1955 and 2011 that tested the effect of garlic preparations on serum lipid concentrations (93). These 39 trials studied 2,298 adult participants (mean age, 49.5 years), administered garlic-only preparations, used a true placebo, and lasted for at least two weeks. The majority of included trials recruited subjects with elevated total cholesterol at baseline (>200 mg/dL [>5.2 mmol/L], 29 trials) and lasted more than eight weeks (30 trials). The authors found that garlic preparations significantly lowered total cholesterol and low-density lipoprotein (LDL)-cholesterol compared to placebo. High-density lipoprotein (HDL)-cholesterol concentrations were mildly increased and triglyceride concentrations were not affected by garlic supplementation. All administered garlic preparations (garlic powder, aged garlic extract, garlic oil, and fresh garlic) were well tolerated and associated with only minor side effects (garlic odor and mild gastrointestinal discomfort) (93).

Although garlic supplementation for a minimum of two months may lower total- and LDL-cholesterol concentrations in individuals with elevated total cholesterol, the benefits may not last beyond the short term (90, 92). Whether garlic possesses long-lasting lipid-lowering effects remain questionable and future investigations may focus on ways to maximize potential benefits of garlic preparations on serum lipids.

Atherosclerosis

Very few studies have attempted to assess the effect of garlic supplementation on the progression of atherosclerosis in humans. One early study in Germany used ultrasound imaging to assess the effect of 900 mg/day of dehydrated garlic on the progression of atherosclerotic plaque in the carotid and femoral arteries (94). After four years, the increase in plaque volume was significantly greater in women taking the placebo (+53.1%) than in women taking the garlic supplement (-4.6%), while no significant difference in plaque volume was found between garlic (+1.1%) and placebo (+5.5%) in men (94, 95). In a smaller pilot study, investigators measured coronary artery calcium using electron-beam computed tomography to assess the effect of supplementation with aged garlic extract on the progression of atherosclerosis in 19 adults already taking HMG-CoA reductase inhibitors (lipid-lowering drugs also known as statins) (18). After one year, increases in coronary artery calcium score were significantly lower in those taking aged garlic extract than in those taking a placebo. Nevertheless, although coronary calcium scores may have a predictive value regarding future cardiac events in asymptomatic subjects, it may not be a reliable marker of plaque burden in symptomatic patients (96, 97). In a recent double-blind, controlled study, the extent of coronary atherosclerosis was assessed with cardiac computed tomography angiography in 72 individuals (55 at study completion) at high risk of coronary heart disease randomized to receive either 2,400 mg of aged garlic extract or placebo for 52 weeks (98). The result suggested a significant decrease in the extent of coronary plaques with low-attenuation area (a type of vulnerable plaques prone to rupture) (99, 100) with aged garlic extract compared to placebo, but no differences in total plaque volume and proportions of non-calcified plaques and dense calcium were found between treatment and placebo groups (98).

Hypertension

Most systematic reviews and/or meta-analyses of randomized controlled trials to date have provided mixed results regarding the potential blood pressure-lowering effect of garlic, possibly because most of these trials enrolled both normotensive and hypertensive subjects (90, 101-105).

A systematic review and meta-analysis by Xiong et al. (106) included seven randomized, placebo-controlled trials that exclusively enrolled individuals with high blood pressure, i.e., with systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg. Five out of seven trials identified in this systematic review reported statistically significant reductions in SBP and DBP with several garlic preparations (dried garlic homogenate, garlic powder, and aged garlic extract) (106). Another recent meta-analysis included nine randomized controlled trials in 482 hypertensive individuals who were given garlic powder (six studies), garlic homogenate (one study), aged garlic extract (two studies), or placebo for 8 to 26 weeks (107). Garlic preparations were found to significantly reduce SBP by a mean of 9.1 mm Hg and DBP by a mean of 3.8 mm Hg compared to placebo. The most recent meta-analysis found that garlic preparations reduced SBP by a mean 8.7 mm Hg (10 trials, 440 subjects) and DBP by 6.1 mm Hg (8 trials, 257 subjects) (102). Such reductions in blood pressure seem comparable to those reported with currently used classes of blood pressure-lowering medications (average reduction, -9.1 mm Hg for SBP and -5.5 mm Hg for DBP) (108). The effect of blood pressure reduction from such medications at standard dose has been estimated to lower the risk of coronary heart disease events by about one-quarter and the risk of stroke by about one-third (108). Nonetheless, evidence showing that garlic supplements may reduce the risk of cardiovascular morbidity and mortality is still lacking (109).

In a recent 12-week, randomized, placebo-controlled trial in untreated hypertensive subjects, daily intake of aged garlic extract (1.2 g of which contained 1.2 mg of S-allyl-L-cysteine [SAC]) was shown to significantly lower SBP by 11 mm Hg and DBP by 6 mm Hg on average in 50%-60% of participants, but reductions in blood pressure were not reported in 40%-50% of participants compared to placebo (110). Whether interindividual differences in nutritional status and genetic polymorphisms can explain differences in blood pressure response to garlic treatment need to be explored in future studies (53, 110).

Overall, short-term garlic supplementation appears to effectively reduce blood pressure with minimal side effects in hypertensive patients.

Summary

The results of randomized controlled trials have suggested that garlic supplementation modestly improves serum lipid profiles in individuals with elevated serum cholesterol and reduces blood pressure in hypertensive subjects. It is not yet clear whether garlic supplementation can reduce atherosclerosis or prevent cardiovascular events, such as myocardial infarction or stroke pressure in hypertensive subjects. It is not yet clear whether garlic supplementation can reduce atherosclerosis or prevent cardiovascular events, such as myocardial infarction or stroke.

Cancer

Gastric cancer

A recent meta-analysis of 17 studies (mostly case-control studies) reported an inverse association between high versus low garlic consumption and the risk of gastric cancer (111). Nevertheless, this conclusion is hindered by a number of limitations, especially related to the retrospective design of most studies included in the analysis, as well as great variations in the amount and duration of garlic intakes. In a 2009 review of the literature, Kim et al. (112) identified 20 human studies that examined garlic intake in relation to gastric cancer risk: three intervention studies, one case-cohort study, 13 case-control studies, and three cross-sectional/ecologic studies. Using the Food and Drug Administration (FDA)'s evidence-based criteria for the scientific evaluation of health claims (113), the authors excluded 16 studies for methodological flaws; only four studies (two case-control (114, 115), one case-cohort (116), and one intervention (85)) received moderate-to-high quality ratings (112). Among these four studies, garlic intake during adolescence or 20 years prior to the interview was not found to be associated with the risk of gastric cancer in one of the case-control studies in Sweden (338 gastric cancer patients and 669 control subjects) (114). Another case-control study in Korea failed to show an association between past garlic consumption and gastric cancer in 136 people diagnosed with gastric cancer and 136 cancer-free subjects (115). In addition, a prospective case-cohort study in the Netherlands found no association between the use of garlic supplements (unknown composition) and gastric cancer risk (116). Finally, a randomized, double-blind, placebo-controlled intervention study in 3,365 subjects from the Shandong province of China found that supplementation with aged garlic extract and steam-distilled garlic oil for 7.3 years did not reduce the prevalence of precancerous gastric lesions or the incidence of gastric cancer (85). An updated analysis of the data collected 7.3 years after garlic supplementation ended provided further confirmation for a lack of significant reduction in gastric cancer incidence or mortality with supplemental garlic (117).

***Helicobacter pylori* (*H. pylori*) infection and gastric cancer**: Infection with some strains of *H. pylori* bacteria markedly increases the risk of gastric cancer. Although garlic preparations and organosulfur compounds could inhibit the growth of *H. pylori* in the laboratory (118, 119), there is little evidence to suggest that high garlic intakes or garlic supplementation may help prevent or eradicate *H. pylori* infection in humans (120). Higher intakes of garlic were not associated with a significantly lower prevalence of *H. pylori* infection in China or Turkey (121, 122). Moreover, clinical trials using garlic cloves (123), aged garlic extract (84), steam-distilled garlic oil (84, 124), garlic oil macerate (125), or garlic powder (126) have not found garlic supplementation to be effective in eradicating *H. pylori* infection in humans.

Colorectal cancer

A 2014 meta-analysis of prospective cohort studies in 335,923 subjects (including 4,610 colorectal cancer [CRC] cases) found no association of consuming raw or cooked garlic (three studies, four cohorts) or supplemental garlic (four studies, five cohorts) with CRC (127). Another recent systematic review and meta-analysis that combined data from seven cohort and seven case-control studies also failed to find a statistically significant reduction in CRC risk with garlic intake (128). Yet, these results are in contrast with previous pooled analyses of data from case-control studies (129) or from both case-control and prospective studies (130) that reported an approximate 30% lower CRC risk in individuals with the highest garlic intakes compared to those with the lowest intakes. Inclusion of case-control studies, which are more susceptible to bias, may explain these discrepancies among meta-analyses (128). For information regarding different types of epidemiological studies, see the Spring/Summer 2016 LPI Research Newsletter.

A small preliminary intervention trial in 37 patients with colorectal adenomas examined whether supplementation with aged garlic extract for 12 months affected adenoma size and recurrence. Both the number and size of adenomas were significantly reduced in patients given a high dose of aged garlic extract compared to those given a much lower dose (0.16 mL/day) (131, 132). Larger randomized controlled trials are needed to determine whether garlic or garlic extracts can substantially reduce adenoma progression to advanced cancer and recurrence.

Other types of cancer

In a small, placebo-controlled intervention study in 50 patients with cancer (42 with liver cancer, seven with pancreatic cancer, and one with colon cancer), supplementation with 500 mg/day of aged garlic extract for six months failed to prevent quality of life deterioration caused by disease progression and chemotherapy-associated adverse effects (133). Yet, the active treatment limited the decline in natural killer cell count and activity that accompanies digestive cancer progression and reduces patient survival (133).

At present, evidence from trials is limited and results from observational studies do not suggest a role of high intakes of garlic in the prevention of cancer in humans (112).

Sources

Food sources

Allium vegetables, including garlic and onions, are the richest sources of organosulfur compounds in the human diet (134). To date, the majority of scientific research relating to the health effects of organosulfur compounds has focused on those derived from garlic. Fresh garlic cloves contain about 2 to 6 mg/g of γ-glutamyl-S-allyl-L-cysteine (0.2%-0.6% fresh weight) and 6 to 14 mg/g of alliin (0.6%-1.4% fresh weight). Garlic cloves yield about 2.5 to 4.5 mg of allicin per gram of fresh weight when crushed. One fresh garlic clove weighs 2 to 4 g (5).

Effects of cooking

The enzyme alliinase can be inactivated by heat. In one study, microwave cooking of unpeeled, uncrushed garlic totally destroyed alliinase enzyme activity (135). An *in vitro* study found that prolonged oven heating or boiling (i.e., six minutes or longer) suppressed the inhibitory effect of uncrushed and crushed garlic on platelet aggregation, but crushed garlic retained more anti-aggregatory activity compared to uncrushed garlic (136). Administering raw garlic to rats significantly decreased the amount of DNA damage caused by a chemical carcinogen, but heating uncrushed garlic cloves for 60 seconds in a microwave oven or 45 minutes in a convection oven prior to administration blocked the protective effect of garlic (137). The protective effect of garlic against DNA damage can be partially conserved by crushing garlic and allowing it to stand for 10 minutes prior to microwave heating for 60 seconds or by cutting the tops off garlic cloves and allowing them to stand for 10 minutes before heating in a convection oven. Because organosulfur compounds derived from alliinase-catalyzed reactions may play a role in some of the biological effects of garlic, some scientists recommend that crushed or chopped garlic be allowed to "stand" for at least 10 minutes prior to cooking (135).

Supplements

Several different types of garlic preparations are available commercially, and each type provides a different profile of organosulfur compounds depending on how it was processed (see **Table 1**). Not all garlic preparations are standardized, and even standardized brands may vary with respect to the amount and the bioavailability of the organosulfur compounds they provide (5).

Powdered (dehydrated) garlic

Powdered or dehydrated garlic is made from garlic cloves that are usually sliced and dried at a low temperature to prevent alliinase inactivation (138). The dried garlic is pulverized and often made into tablets. To meet United States Pharmacopeial Convention (USP) standards, powdered garlic supplements must contain no less than 0.1% γ-glutamyl-S-allyl-L-cysteine and no less than 0.3% alliin (dry weight) (139). Although powdered garlic supplements do not actually contain allicin, the manufacturer may provide a value for the "allicin potential" or "allicin yield" of a supplement on the label. These values represent the maximum achievable allicin yield of a supplement (140). It is determined by dissolving powdered garlic in water at room temperature and measuring the allicin content after 30 minutes (139). Because alliinase is inactivated by the acidic pH of the stomach, most powdered garlic tablets are enteric-coated to keep them from dissolving before they reach the neutral pH of the small intestine. It has been argued that it is more appropriate to measure "allicin release" using a USP method for assessing drug release from enteric-coated tablets under conditions that mimic those of the stomach and intestine (139). Allicin release by this method has been shown to parallel true bioavailability (140). Most tablet brands have been found to produce little allicin under these conditions, due mainly to low alliinase activity and prolonged disintegration times (140, 141). Many manufacturers provide information on the "allicin potential" of their powdered garlic supplements, but few provide information on the "allicin release." A number of controlled clinical trials have examined the effect of powdered or dehydrated garlic supplements on cardiovascular risk factors (see Cardiovascular disease). The most commonly used doses ranged from of 600 to 900 mg/day and provided 3.6 to 5.4 mg/day of potential allicin (90).

Garlic fluid extracts (aged garlic extract™)

When garlic cloves are incubated in a solution of ethanol and water for up to 20 months, allicin is mainly converted to allyl sulfides, which are lost by evaporation or converted to other compounds (138). The resulting extract contains primarily water-soluble organosulfur compounds, such as SAC and SAMC (see **Figure 3**) (142). Garlic fluid extracts, including aged garlic extracts, are standardized to their S-allyl-L-cysteine content. In controlled clinical trials, daily intakes of aged garlic extract at doses between 1.2 g-2.4 g (containing 1.2 to 2.4 mg of S-allyl-L-cysteine) consistently resulted in reductions in SBP by 9 mm Hg-10 mm Hg and reductions in DBP by 4 mm Hg-8 mm Hg in a majority of patients with uncontrolled hypertension (110, 143). Additionally, aged garlic extract at doses of 2.4 to 7.2 g/day resulted in short-term reductions in *ex vivo* platelet aggregation (144) and reductions in serum cholesterol concentrations up to 12 weeks (16).

Steam-distilled garlic oil

Steam distillation of crushed garlic cloves results in a product that contains mainly allyl sulfides, including DATS, DADS, and DAS (see **Figure 2**) (138). These fat-soluble steam distillation products are usually dissolved in vegetable oil.

Garlic oil macerates

Incubation of crushed garlic cloves in oil at room temperature results in the formation of vinyldithiins and ajoene from allicin, in addition to allyl sulfides, such as DADS and DATS (see **Figure 2**) (5). Ether extracts are similar in composition to garlic oil macerates but more concentrated (145).

Table 1. Principal Organosulfur Compounds in Commercial Garlic Preparations (4, 6)

Product	Principal Organosulfur Compounds	Delivers Allicin-derived Compounds?
Fresh garlic cloves	Cysteine sulfoxides (Alliin) γ-Glutamyl-L-cysteine peptides	Yes, when chopped, crushed, or chewed raw. Minimal, when garlic cloves are cooked before crushing or chopping.
Garlic powder (tablets)	Cysteine sulfoxides (Alliin) γ-Glutamyl-L-cysteine peptides	Varies greatly among commercial products. Enteric-coated tablets that pass the USP allicin release test are likely to provide the most.
Steam-distilled garlic oil (capsules)	Diallyl disulfide (DADS) Diallyl trisulfide (DATS) Allyl methyl trisulfide	Yes, but there is only 1% of oil-soluble sulfur compounds in 99% of vegetable oil.
Garlic oil macerate (capsules)	Vinyldithiins (E/Z)-ajoene Diallyl trisulfide	Yes
Aged garlic extract™ (tablets or capsules)	S-Allyl-L-cysteine (SAC) S-Allylmercaptocysteine (SAMC) *trans*-S-1-Propenyl-L-cysteine	Minimal

Safety

Adverse effects

The most commonly reported adverse effects of oral ingestion of garlic and garlic supplements are breath and body odor (90, 146). Gastrointestinal symptoms have also been reported, including heartburn, abdominal pain, belching, nausea, vomiting, flatulence, constipation, and diarrhea (106). The most serious adverse effects associated with oral garlic supplementation are related to uncontrolled bleeding. Several cases of serious postoperative or spontaneous bleeding associated with garlic supplementation have been reported in the medical literature (147-150). Garlic may also trigger allergic responses in some individuals, including asthma in people with occupational exposure to garlic powder or dust (151). Exposure of the skin to garlic has been reported to cause contact dermatitis in some individuals (146, 152). More serious skin lesions, including blisters and burns, have also been reported with topical exposure to garlic for six or more hours.

The safety characteristics of the various garlic preparations likely depend on their specific chemical composition (see **Table 1**). Aged garlic extract — the only water-based garlic supplement — showed a safe profile in toxicity studies and exhibited no undesirable side effects when combined with anticoagulants (warfarin), antiplatelets (aspirin), cholesterol-lowering (statins) drugs, or anticancer drugs (doxorubicin, 5-fluorouracil, methotrexate) in clinical settings (reviewed in 6). Safety and toxicity data are lacking for lipophilic (hydrophobic) garlic preparations, but some of their constituents have been shown to interfere with drug-metabolizing enzymes and transporters (see Drug interactions).

Pregnancy and lactation

No adverse effects on pregnancy outcomes have been reported when garlic is consumed in the diet. Although no adverse pregnancy outcomes were reported in a study of Iranian women who took dehydrated garlic tablets (800 mg/day) for two months during the third trimester of pregnancy (153), the safety of garlic supplements in pregnancy has not been established. There is some evidence that garlic consumption alters the odor and possibly the flavor of breast milk. In a controlled cross-over trial, oral consumption of 1.5 g of garlic extract by lactating women increased the perceived intensity of breast milk odor (154). Infants spent more time breast-feeding after their mothers consumed the garlic extract compared to a placebo, but the amount of milk consumed and number of feedings were not significantly different. Additionally, it is not known if topical use of garlic is safe during pregnancy or lactation.

Drug interactions

Anticoagulant medications

Garlic may enhance the anticoagulant effects of warfarin (Coumadin). There have been two case reports in which prothrombin time (INR) increased in patients who started taking garlic tablets or garlic oil without changing their warfarin dose or other habits (155). However, a more recent study in closely monitored patients on warfarin therapy found that garlic fluid extracts (aged garlic extract) did not increase hemorrhagic risk (156). Since garlic supplements have been found to inhibit platelet aggregation (90), there is a potential for additive effects when garlic supplements are taken together with other medications or supplements that inhibit platelet aggregation, such as high-dose fish oil or vitamin E (157). More research is needed to determine whether garlic supplements are safe for people on anticoagulatory therapy.

HIV protease inhibitors

Supplementation of healthy volunteers with garlic caplets twice daily (allicin yield, 7.2 mg/day) for three weeks resulted in a 50% decrease in the bioavailability of the protease inhibitor, saquinavir (Fortovase) (158). Although saquinavir undergoes significant metabolism by CYP3A4, supplementation with garlic extract for two weeks did not significantly alter a measure of CYP3A4 activity in healthy volunteers (159). Garlic extract supplementation (10 mg/day) for four days did not significantly alter single-dose pharmacokinetics of the protease inhibitor, ritonavir (Norvir), but further research is needed to determine steady-state interactions between well-characterized garlic supplements and ritonavir (160). *In vitro* hepatic models suggested that flavonoids and sulfur-containing compounds in garlic supplements might interfere with the activity of efflux drug transporters of the ATP-binding cassette (ABC) family, including P-glycoprotein, multidrug resistance protein (MRP), and breast cancer-resistance protein (BCRP), which function as ATP-dependent efflux pumps that actively regulate the excretion of a number of drugs limiting their systemic bioavailability. They may also affect the activity of phase I biotransformation enzymes like cytochrome P450 (CYP) 3A4 (CYP3A4) (161, 162). Modifications of efflux transporter and CYP3A4 activities may explain how supplementation with garlic phytochemicals might hinder the therapeutic efficacy of medications like antiretroviral drugs (162).

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Legumes

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Summary

- Foods from the legume family include beans, peas, lentils, peanuts, and soybeans. *(More information)*
- Legumes are excellent sources of protein, low-glycemic index carbohydrates, essential micronutrients, and fiber. *(More information)*
- Substituting legumes for foods that are high in saturated fats or refined carbohydrates is likely to lower the risk of cardiovascular disease and type 2 diabetes mellitus. *(More information)*
- Regular consumption of legumes, both pulses (legumes excluding green peas, green beans, peanuts, and soybeans) and soy food, may result in favorable effects on blood lipid profiles by lowering LDL-cholesterol. *(More information)*
- Several observational studies have found non-soy legume intake to be inversely associated with incidence of prostate cancer. *(More information)*
- Lifelong exposure to soy food may be needed to lower risk of breast cancer. *(More information)*
- Short-term clinical trials have reported pulse consumption increases satiety; however, high-quality trials are needed to determine whether regular consumption of pulses results in weight loss in the long term. *(More information)*
- The most recent Dietary Guidelines for Americans include legumes in both the protein and vegetable groups, recommending a weekly intake of 1½ to 3 cup-equivalents of legumes for those who consume 2,000 calories/day. This recommended amount depends on the specific dietary pattern followed, and additionally, soy products are recommended for those who follow a vegetarian diet. *(More information)*

Introduction

Legumes are plants of the Leguminosae family with seed pods that split into two halves. Edible seeds from plants of this family include beans, peas, lentils, soybeans, and peanuts. The most recent Dietary Guidelines for Americans do not include green peas or green (string) beans as legumes due to a dissimilar nutritional profile when compared to the other legume family members (1). Peanuts are nutritionally similar to tree nuts; therefore, information on their health effects is presented in a separate article on Nuts and not discussed below. Many studies have examined how the consumption of pulses is related to health; pulses are legumes harvested as dry grain and thus exclude green peas, green beans, as well as crops used for oil extraction (soybeans, peanuts) (2).

Although legumes are an important part of traditional diets around the world, they are often neglected in typical Western diets. Legumes are inexpensive, nutrient-dense sources of protein that can be substituted for dietary animal protein (3). While sources of animal protein are often rich in saturated fats, the small quantities of fats in legumes are mostly unsaturated fats. Legumes are also good sources of several essential minerals, rich in dietary fiber (both soluble fiber and resistant starch), and considered to be low-glycemic index foods (4, 5). Moreover, legumes contain numerous phytochemicals that may affect health. Soybeans have attracted the most scientific interest, mainly because they are a unique source of phytoestrogens known as isoflavones (6). Overall, legumes represent unique packages of nutrients and phytochemicals that may work synergistically to reduce risk of chronic disease, as other edible seeds do (7).

Note: Research on the health effects of diets rich in legumes, including peas and soy foods, is summarized below. For a discussion of the potential health benefits and risks of soy isoflavones, see the separate article on Soy Isoflavones.

Disease Prevention

Type 2 diabetes mellitus

Consumption of legumes, which are rich in dietary fiber, other nutrients, and bioactive compounds, might help improve insulin sensitivity and regulate blood glucose concentrations, thereby influencing risk of type 2 diabetes mellitus.

Beans, peas, and lentils

The glycemic index is a measure of the potential for carbohydrates in different foods to raise blood glucose concentrations. In general, consuming foods with high-glycemic index values causes blood glucose concentrations to rise more rapidly, which results in greater insulin secretion by the pancreas, than after consuming foods with low-glycemic index values. Chronically elevated blood glucose concentrations and excessive insulin secretion are thought to play important roles in the development of type 2 diabetes mellitus (8). Low-glycemic load diets have been associated with reduced risk of developing type 2 diabetes in some, but not all, prospective cohort studies (see the article on Glycemic Index and Glycemic Load). High-fiber diets have also been associated with a decreased risk of type 2 diabetes (see the article on Fiber).

Together, the high-fiber content and low-glycemic index nature of legumes may contribute to help lower risk of type 2 diabetes in those who incorporate them into their daily diets. However, a 2017 meta-analysis of 12 prospective cohort studies found that higher legume intakes were not associated with risk of developing type 2 diabetes compared to lower intakes (range, 0-190 g/day; ~0-2 servings/day) (9), although a more recent prospective study not included in this pooled analysis found an inverse association (10).

Results of clinical trials of legume or pulse consumption have been more promising. A meta-analysis of 41 randomized controlled trials (some in individuals with normoglycemia and some in individuals with type 1 or type 2 diabetes) found that pulse consumption, either alone or in combination with a low-glycemic index diet or a high-fiber diet, improved some measures of glucose control, including fasting blood glucose and insulin concentrations, as well as markers of long-term glycemic control (11). The effect was stronger in patients with diagnosed diabetes compared to individuals with normoglycemia (11). In a three-month trial in 114 people with type 2 diabetes, those randomized to a low-glycemic diet that emphasized 1 cup/day of legumes had significant improvements in their hemoglobin A_{1C} value — the main fraction of glycated hemoglobin that reflects glycemic control over the past four months — compared to those randomized to a high-wheat fiber diet (12).

Small studies in healthy individuals have found that consumption of legumes improved postprandial glucose response at the subsequent meal (called the 'subsequent meal effect' or 'second meal effect') (13-15), although this has not been extensively studied. In addition to improving glycemic and insulin control, consumption of legumes may increase satiety and decrease both food intake and body weight, indirectly improving glycemic control (see Obesity below).

Soy

Observational studies on the association of soy intake and type 2 diabetes mellitus have reported mixed results. A 2018 meta-analysis of eight observational studies (six prospective cohort and two cross sectional) found an inverse association between soy intake and risk of type 2 diabetes; however, there was a high degree of heterogeneity in the analysis (16). Moreover, when a subgroup analysis was done and only prospective cohort studies were examined, the association was no longer significant (16).

A meta-analysis of 19 randomized controlled trials, including 1,518 participants, found that soy consumption — as soy foods/whole soy, isolated soy protein, or soy isoflavone supplements — had no effect on fasting glucose or insulin concentrations (17). Yet, subgroup analyses reported the effect on hyperglycemia differed by type of soy intervention: adherence to a whole-soy diet lowered fasting glucose concentrations, while soy protein isolate or isoflavone supplementation had no effect on fasting glucose concentrations (17).

Cardiovascular disease

Several characteristics of legumes may contribute to protection against cardiovascular disease. They are rich in soluble fiber and phytosterols, which are known to have cholesterol-lowering effects, and their high folate content may help lower homocysteine concentrations. Additionally, legumes are good sources of magnesium and potassium, which may decrease cardiovascular disease risk by helping to lower blood pressure (18). The low-glycemic index values of beans mean that they are less likely to raise blood glucose and insulin concentrations (see Type 2 diabetes mellitus above), and this may also decrease cardiovascular disease risk. Further, the substitution of legumes for foods high in saturated fat or refined carbohydrates may offer some cardioprotection.

Beans, peas, and lentils

Some, but not all, observational studies have found regular legume intake to be associated with a lower risk of cardiovascular events, and overall, most clinical trials have found legume consumption decreases cardiometabolic risk factors, especially circulating LDL-cholesterol concentrations. In a meta-analysis of eight prospective cohort studies, legume intake as part of a Mediterranean diet was associated with a 9% lower risk of cardiovascular disease, although one of the included studies grouped legume consumption with nuts, which are known to be cardioprotective (see the article on Nuts) (19). In a systematic review and meta-analysis of five prospective cohort studies, consuming four 100-g servings of legumes (beans, peas, lentils, tofu) weekly was associated with a 14% lower risk of coronary heart disease (CHD) (20). This association was driven mainly by a prospective cohort study that followed participants for 19 years, finding those who ate dry beans, peas, or peanuts at least four times weekly had a 21% lower CHD risk compared to those who ate them less than once weekly (21). Most recently, in a meta-analysis that included both CHD incidence and CHD-related mortality together as outcomes (eight prospective cohort studies in total), the highest versus lowest legume intakes were associated with a 10% decreased risk (22). In contrast, legume intake has not been linked to risk of stroke in four separate meta-analyses (20, 22-24).

Serum lipid profiles: Some, but not all, clinical trials have found that regular legume consumption results in favorable changes in the lipid profile. A 2014 systematic review and meta-analysis of 26 randomized controlled trials reported that pulse intake (beans, lentils, peas; median intake of 130 g/day or ~1.3 servings/day) reduced LDL-cholesterol concentrations by 0.17 mmol/L (6.6 mg/dL) compared to an isocaloric diet without pulses; however, there was no effect of pulse intake on non-HDL cholesterol or apolipoprotein B concentrations (25). It is important to note that there was significant heterogeneity among included trials of this meta-analysis, and the baseline lipid status of participants varied among the trials: eight trials included hyperlipidemic subjects, three trials were done in participants with normal lipid profiles, and 15 trials had a combination of normal and high lipid levels (25). A previous meta-analysis of randomized controlled trials found that non-soy legume consumption decreased total and LDL-cholesterol concentrations by 11.76 mg/dL (10 studies) and 7.98 mg/dL (9 studies), respectively, when compared to a matched control (matched for total calories or macronutrients; baseline total cholesterol concentrations of participants ranged from 199 to 295 mg/dL among studies) (26). A trend for a reduction in serum triglycerides (-18.94 mg/dL, p=0.05) was observed in this meta-analysis, and no effect on HDL cholesterol was found (26).

Hypertension: Adherence to the Dietary Approaches to Stop Hypertension (DASH) eating plan, which includes dry beans and peas among many other components (27), has been shown to reduce blood pressure (28), but it is not known whether legumes contribute to this effect. A 2014 meta-analysis of eight isocaloric, controlled feeding trials (median of 10 weeks' duration) — including both normotensive and hypertensive participants (n=554; median age, 49 years) — found that pulse consumption (median of 162 g/day or ~1.6 daily servings) decreased systolic blood pressure by 2.25 mm Hg but had no effect on diastolic blood pressure (29). It is important to note that there was significant heterogeneity among trials included in the meta-analysis (29).

Soy

Serum lipid profiles: In 1999, the US Food and Drug Administration (FDA) approved the following health claim: "Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease" (30). Most of the evidence to support this health claim was included in the Anderson et al. meta-analysis of 38 controlled clinical trials that was published in 1995. This meta-analysis found that an average intake of 47 g/day of soy protein decreased serum total cholesterol concentrations by an average of 9% and LDL-cholesterol concentrations by an average of 13% (31). Hypocholesterolemic effects were primarily noted in individuals with high baseline cholesterol concentrations (31). A meta-analysis of 33 studies published since 1995 confirmed the hypocholesterolemic effect of soy protein reported in the Anderson et al. publication (32). Another meta-analysis of 30 studies in individuals with normal or mildly elevated cholesterol levels concluded that about 25 g/day of soy protein significantly lowers LDL-cholesterol concentrations by about 6% (33). Yet, a 2006 science advisory from the Nutrition Committee of the American Heart Association concluded that earlier research indicating that soy protein consumption results in clinically important reductions in LDL-cholesterol compared to other proteins has not been confirmed (34). A 2011 meta-analysis of randomized controlled trials, mostly in participants with hypercholesterolemia, found consumption of soy protein decreased LDL-cholesterol by 5.5% in parallel-design studies (20 trials; median soy protein intake of 31.5 g/day for a mean of 9.2 weeks) and 4.2% in cross-over studies (23 trials; median soy protein intake of 26.0 g/day for a mean of 6.0 weeks) — such decreases may translate to 6%-10% decreases in risk for coronary heart disease (35).

Consumption of isolated soy isoflavones (as supplements or extracts), however, does not appear to have favorable effects on serum lipid profiles (35-42).

In addition to possibly lowering cholesterol, incorporating soy foods into the diet may benefit overall cardiovascular health due to their relatively high content of polyunsaturated fat, fiber, and phytosterols compared to animal products (43).

Cancer

Legumes

Colorectal cancer: Legumes, including soybeans, contain fermentable dietary fiber and certain micronutrients and phytochemicals that may have anticancer effects. Some legumes contain serine protease inhibitors of the "Bowman-Birk family" (called Bowman-Birk inhibitors) that may have potential chemopreventive effects in the large intestine (44). Moreover, simply replacing red and processed meats, which are linked to a higher risk of colorectal cancer (45), with legumes in the diet might lower risk.

To date, observational studies of legume intake and colorectal cancer have reported conflicting findings. A meta-analysis of 14 prospective cohort studies found that higher legume intake was linked to a 9% lower risk of colorectal cancer, although there was significant heterogeneity among studies (46). Subgroup analyses revealed an inverse association between soybeans and colorectal cancer (RR, 0.85; 95% CI, 0.73-0.99) but not with dry beans and colorectal cancer (RR, 1.00; 95% CI, 0.89-1.13) (46). An earlier meta-analysis of cohort and case-control studies found that higher versus lower legume intake was associated with a 17% lower risk of colorectal adenoma (47).

Beans, peas, and lentils

Although beans, peas, and lentils are rich in a number of compounds that could potentially reduce the risk of certain cancers, the results of observational studies are too inconsistent to draw any firm conclusions regarding bean intake and cancer risk in general (48, 49).

Prostate cancer: Several prospective cohort studies have found non-soy legume intake to be inversely related to incidence of prostate cancer. In a six-year prospective study of more than 14,000 Seventh Day Adventist men living in the United States, those with the highest intakes of legumes (beans, lentils, or split peas) had a 47% lower risk of prostate cancer (50). In a prospective study of more than 58,000 men in the Netherlands, those with the highest intakes (median intake, 62 g/day) of legumes (including pulses and dried seeds) had a risk of prostate cancer that was 29% lower than those with the lowest intakes (median intake, 11 g/day) (51). Moreover, a prospective study in a multiethnic cohort of 82,483 men examined the risk of prostate cancer in men who consumed legumes excluding soy products. In this study, men who consumed the highest amount of non-soy legumes had a 10% lower risk of total prostate cancer and a 28% lower risk of nonlocalized or high-grade prostate cancer compared to those who consumed the least amount of non-soy legumes (52). However, another study found no association between dry bean intake and prostate cancer (53). Most recently, in a prospective study in 3,313 French men, non-soy legume consumption was linked to a 44% reduced risk of prostate cancer (54). A meta-analysis of these five prospective cohort studies found legume consumption was associated with a 15% lower risk of prostate cancer development (95% CI, 0.72-0.99) (55). Moreover, a pooled analysis of 13 prospective cohort studies found a similar association: a 14% lower risk of prostate cancer in men who consumed ≥100 g/day of mature beans (all beans excluding green beans and soybeans) compared to those who had intakes lower than 15 g/day (56).

Soy

Prostate cancer: Incidence rates of prostate cancer are much higher in North America, Northern and Western Europe, Australia, and New Zealand compared to Asian countries, such as Japan and China, where soy is common in the diet (57). Soy food consumption has been associated with a reduced risk of prostate cancer in pooled analyses of observational studies (58-62). In the most recent meta-analysis, total soy intake (16 studies) and unfermented soy intake (11 studies) were associated with a 29% and 35% lower risk of prostate cancer, respectively; no association was found between fermented soy intake and prostate cancer (eight studies) (62). Subgroup analyses revealed that the protective association of total soy intake was much stronger in case-control (39% lower risk) versus prospective cohort and nested case-control studies (10% lower risk) — unfermented soy intake was only associated with prostate cancer risk in case-control studies (45% lower risk) (62). Results of case-control studies are more likely to be distorted by bias (i.e., the selection bias with the selection of cases and controls, as well as dietary recall bias) than results of prospective cohort studies.

For a review of studies on soy isoflavone intake and prostate cancer, see the separate article on Soy Isoflavones.

Breast cancer: More than 25 observational studies have assessed the relationship between soy food intake and the risk of breast cancer. A 2008 meta-analysis of prospective cohort studies and case-control studies reported differential effects based on the typical level of soy consumption (63). In Asian populations, where soy intake is high, the authors found an inverse association between soy food intake and breast cancer; however, no association was observed in studies completed in Western populations, where soy food intake is much lower (63). A 2016 meta-analysis of 10 prospective cohort studies — four conducted in Japan, three in the US, two in China, and one in France — found that higher intake of soy food was associated with an 8% lower incidence of breast cancer compared to lower intake (64).

Age at exposure to soy might affect subsequent risk of developing breast cancer. For instance, a few case-control studies have reported that higher soy intake during childhood or adolescence was associated with a lower risk of developing breast cancer later in life (65-68). Soy intake later in life may not have as strong as an effect on breast cancer compared to exposure during childhood and adolescence (63), and lifelong exposure to soy food may be needed to lower risk of breast cancer (69).

Isoflavones are likely responsible for any protection of soy against the development of breast cancer; studies of soy isoflavone intake and breast cancer are reviewed in the separate article on Soy Isoflavones.

Endometrial cancer: Since soy isoflavones have estrogenic activity, studies have investigated whether isoflavone intake from soy food or supplements might be related to development of endometrial cancer. There is only limited evidence of an inverse association, primarily from case-control studies (70); see the separate article on Soy Isoflavones.

Gastrointestinal cancers: Results of observational studies examining soy intake and gastrointestinal cancers, including gastric cancer and colorectal cancer, have been mixed. A 2016 meta-analysis that included 18 case-control and 16 prospective cohort studies found soy consumption was associated with a 7% lower risk of gastrointestinal cancer; however, soy intake was not significantly linked to gastrointestinal cancer when the data from only cohort studies were considered (OR, 0.97; 95% CI, 0.90-1.03) (71). A separate meta-analysis reported soybean intake was associated with a 15% lower risk of colorectal cancer (95% CI, 0.73-0.99), but only three prospective cohort studies were included in this analysis (46). High-quality studies that control for potential confounders are needed to determine whether soy food intake — or legume intake in general — is linked to a lower risk of gastric or colorectal cancer.

Obesity

Numerous clinical trials have shown that consuming low-glycemic index food delays the return of hunger, decreases subsequent food intake, and increases the sensation of fullness compared to consuming high-glycemic index food (72, 73). Some trials have specifically examined the effect of legume or pulse consumption on food intake amount, satiety, or body weight. A 2016 meta-analysis that included 21 randomized controlled trials, mostly in overweight or obese subjects, reported an overall weight loss of 0.34 kg (0.75 lb) with diets that contained pulses (median intake 132 g/day for a median of six weeks; one serving ~100 g/day) (74). This analysis found a greater weight loss in negative-energy balance trials (i.e., energy-restricted diets; weight loss averaging 1.74 kg or 3.8 lb) than in neutral energy-balance trials (i.e., weight-maintenance diets; weight loss averaging 0.29 kg or 0.64 lb), although both effects were statistically significant (74). Six trials included in this meta-analysis examined the effect of pulse consumption (161 g/day; trial average duration of 10 weeks) on other measures of obesity: no effect was seen on waist circumference, but a trend for reduced body fat percentage was found with pulse consumption (p=0.07) (74). A meta-analysis of 21 controlled clinical trials (duration ranging from 4 weeks to 2 years) found that soy consumption — as whole soy or soy protein — had no effect on body weight, and a subgroup analysis showed that soy consumption actually increased body weight in obese subjects (75). Additionally, this meta-analysis found no effect of soy intake on fat mass (10 trials) or waist circumference (16 trials) (75).

A meta-analysis of nine acute, feeding trials in mostly normal-weight subjects reported pulse consumption, administered as a single bolus, increased measures of satiety by 31% compared to an isocaloric control; however, no effect on food intake at the subsequent/second meal was seen (seven trials) (76). Increases in acute satiety, likely due to the high protein and fiber content and the low-glycemic load of legumes, could lead to reduced food intake and the weight loss observed in some studies. Although currently available studies are limited, the effect on satiety appears to be following consumption of pulses and not soy food (reviewed in 77). High-quality trials are needed to determine whether regular pulse or legume consumption results in weight loss in the long term.

Cognitive health

Some studies have linked adherence to either the Dietary Approaches to Stop Hypertension eating pattern (78, 79) or a Mediterranean-style diet (78, 80-82) with better overall cognitive function in healthy older adults. Legumes are one of many components included in these dietary patterns that might contribute to this purported association; studies reporting specifically on legume intake and cognitive endpoints are limited and have reported mixed results. In a prospective cohort study of 2,613 middle-age and older adults (ages 43-70 years) residing in the Netherlands, followed for five years, legume intake was not associated with changes in global cognitive function (memory, speed of information processing, and cognitive flexibility) (83). In contrast, a prospective, nested case-control study of the Chinese Longitudinal Health Longevity Study found that older adults (≥65 years) who included legumes in their diets nearly every day had a 22% lower risk of cognitive decline over a three-year period compared to those who had lower intakes — this study included 5,691 illiterate older adults who had no evidence of cognitive decline at baseline (84). Most recently, a small study in 214 older, Italian adults (≥65 years) with normal cognitive function used the method of principal component analysis and identified legumes as one of the food categories linked to better cognitive scores at the end of a one-year period (85). Large-scale prospective cohort studies are needed to examine whether legume intake is associated with improvements in cognitive health or risk of dementia in older adults.

Mortality

A 2017 meta-analysis of six prospective cohort studies found a weak, inverse association between legume intake and risk of all-cause mortality (RR: 0.96; 95% CI: 0.94, 1.00) (86). In a large, international prospective cohort study (N=135,335) not included in the 2017 meta-analysis, stronger inverse associations were found with respect to all-cause mortality and non-cardiovascular mortality; however, legume consumption was not associated with cardiovascular-related mortality (87). In this study, consuming more than one serving of legumes daily was associated with a 42% lower risk of non-cardiovascular mortality and a 41% lower risk of all-cause mortality compared to consuming fewer than one legume serving per month (87). In a smaller prospective study (N=7,212) in Spain, conducted among older individuals at high risk for cardiovascular disease, non-soy legume intake was associated with a lower risk of cancer-related mortality but a higher risk of cardiovascular-related mortality (88). It is important to note that average intakes of legumes in this study were low, with those in the highest tertile consuming a mean 28 g/day of legumes — less than one-third of a serving (88). Moreover, a meta-analysis of prospective cohort studies did not find soy intake to be associated with all-cause (six studies), cardiovascular-related (six studies), or cancer-related (eight studies) mortality (89).

Intake Recommendations

Substituting beans, peas, and lentils for foods that are high in saturated fat or refined carbohydrates is likely to help lower the risk of type 2 diabetes mellitus and cardiovascular disease. Soybeans and foods made from soybeans (soy foods) are excellent sources of protein. In fact, soy protein is complete protein, meaning it provides all of the essential amino acids in adequate amounts for human health (6). Like beans, peas, and lentils, soy foods are also excellent substitutes for protein sources that are high in saturated fat like red meat or cheese. Legumes are not only good sources of protein and dietary fiber but also of vitamins, minerals, as well as phytochemicals that may benefit health (see **Table 1**).

The 2015-2020 Dietary Guidelines for Americans — healthy eating recommendations issued jointly by the US Department of Health and Human Services and the US Department of Agriculture — include legumes (beans, lentils, dried peas, and edamame [green soybeans]) in two different food groups: the protein group and the vegetable group (1). Recommended intake of legumes at the 2,000-calorie level translates to 1½ cup-equivalents weekly for those who follow a Healthy US-style or a Healthy Mediterranean-style eating pattern and 3 cup-equivalents weekly for those following a Healthy Vegetarian eating pattern (1). Current intakes of legumes among Americans are well below these recommendations (see Figure 2-4 in the Dietary Guidelines). The Dietary Guidelines also recommend 8 oz-equivalents/week of soy products for vegetarians consuming 2,000 calories/day and 5 oz-equivalents per week for those following other recommended eating patterns, although nuts and seeds can contribute to meet this recommendation. Moreover, fortified soy beverages are emphasized as alternative to dairy in the latest Dietary Guidelines (1).

Table 1. Some Potentially Beneficial Compounds in Legumes

Macronutrients	Vitamins	Minerals	Phytochemicals
Essential Fatty Acids	Folate	Iron	Fiber
	Niacin	Magnesium	Flavonoids
	Riboflavin	Potassium	Lignans
	Vitamin B_6	Zinc	Phytosterols
			Soy Isoflavones

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Nuts

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Summary

- Nuts are good sources of several micronutrients, as well as unsaturated fatty acids, protein, fiber, and phytochemicals. *(More information)*
- Results from large prospective cohort studies show an association between regular nut consumption (≥5 ounces/week) and lower risk of coronary heart disease. There is strong evidence from randomized controlled trials that nut consumption lowers blood cholesterol concentrations. *(More information)*
- There is little evidence to support an association between regular nut consumption and a lower risk of developing type 2 diabetes mellitus. However, there is some evidence suggesting that nut consumption can improve glycemic control in individuals with type 2 diabetes mellitus. *(More information)*
- Current epidemiological data indicate that higher nut consumption does not result in greater weight gain; rather, incorporating nuts into the diet may benefit weight control and contribute to reductions in body weight and waist circumference in energy-restriction diets (i.e., weight-loss diets). *(More information)*
- Meta-analyses of prospective cohort studies show that nut consumption is associated with a reduced risk of all-cause mortality and mortality due to chronic conditions. *(More information)*
- Peanuts and tree nuts can cause life-threatening allergy reactions. Current guidelines for the primary prevention of allergy set by the National Institute of Allergy and Infectious Diseases discourage nut avoidance by non-allergic women during pregnancy and encourage the early introduction to peanuts in age-appropriate foods in infants with no peanut allergy. *(More information)*
- Substituting nuts for unhealthy snacks is a good strategy to avoid weight gain and improve the nutritional quality of one's diet. *(More information)*

Introduction

In the not too distant past, nuts were considered unhealthy because of their relatively high fat content. Recent research, however, suggests that regular nut consumption is an important part of a healthful diet. Although the fat content of nuts is relatively high (13-20 grams (g)/ounce), most of the fats in nuts are monounsaturated and polyunsaturated fats rather than saturated fats (see **Table 1**). The term "nuts" refers to tree nuts like almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pistachios, and walnuts. Despite their name, peanuts are legumes like peas and beans. However, because they are nutritionally similar to tree nuts, they may share some of the same beneficial properties. Studies mentioned in this article have examined the effects of tree nuts and peanuts either together or separately.

Disease Prevention

Cardiovascular disease

In large prospective cohort studies, regular nut consumption has been consistently associated with significant reductions in the risk of coronary heart disease (CHD). An early study that followed more than 30,000 Seventh Day Adventists over 12 years found that participants who consumed nuts at least five times weekly had a 48% lower risk of death from CHD and a 51% lower risk of nonfatal myocardial infarction (MI) compared to those who consumed nuts less than once weekly (1). In addition, the risk of death from CHD was 39% lower in Seventh Day Adventists older than 83 years who ate nuts at least five times weekly compared to those who consumed nuts less than once weekly (2). More recently, an analysis of data from the Nurses' Health Study I that followed 84,136 women (ages at enrollment, 30-55 years) for 26 years reported a 32% lower risk of CHD in those who ate an average of 2.8 servings/week compared to those who never ate nuts (3). A 2014 meta-analysis of 13 prospective cohort studies, including the Seventh Day Adventists and Nurses' Health Studies, found a 34% lower risk of CHD with the highest versus lowest level of nut consumption (4). A dose-response analysis indicated that every 1 serving/week increment in nut consumption was associated with a 5% reduction in CHD risk (4). In another meta-analysis that included data from over 200,000 participants enrolled in three large cohort studies, weekly intake of at least five servings of nuts was associated with a 20% lower risk of CHD when compared to no consumption (5). However, there was no evidence of an association between nut consumption and risk of stroke. In contrast, another recent meta-analysis of prospective cohort studies found a 12% lower risk of stroke (14 studies) and a 19% lower risk of stroke-related death (seven studies) with the highest versus lowest intake of nuts (6).

The PREDIMED (Prevención con Dieta Mediterránea) study that took place between 2003-2011 was a multicenter, randomized controlled trial that examined the effect of a Mediterranean diet, with either extra-virgin olive oil or nuts, compared to a control diet, in the primary prevention of cardiovascular events in 7,447 adults (≥55 years) at high risk of cardiovascular disease (7). Adherence to a Mediterranean diet, supplemented with olive oil or mixed nuts for nearly five years resulted in a 30% lower risk of cardiovascular events and no weight gain (7).

Finally, a modeling study estimated that an increase in daily nut intake from 5 g to 30 g could have prevented 7,680 incidental cardiovascular events and saved about 65,000 years of life that were lost to stroke or heart attack in a scenario based on data from the Swedish population in 2013 (8).

Risk factors

Blood lipids: In a cross-sectional analysis of a representative sample of the US population — the National Health and Nutrition Examination Survey [NHANES] 2005-2010 — tree nut consumers (≥¼ ounce/day) were found to have higher blood HDL-cholesterol concentrations and lower body mass index (BMI), waist circumference, and systolic blood pressure than subjects consuming <¼ ounce/day (9). However, these observations may be due to reverse causation, in particular because health-conscious people are more likely to consume healthy diets that include nuts. A 2015 meta-analysis assessed the evidence of the effect of tree nut consumption on blood lipid profile using findings from 42 randomized controlled studies in a total of 2,101 participants, among which 45% were at risk of cardiovascular disease and untreated. Results indicated lower concentrations of total and LDL-cholesterol concentrations but no effect on concentrations of HDL-cholesterol or triglycerides (10). Similar observations were made in meta-analyses of interventions examining the specific effect of walnut (11, 12), almond (13), hazelnut (14), or pistachio (15) consumption on blood lipid profile of people with normal or elevated blood cholesterol. Interestingly, in a small recent trial in 46 statin-treated participants, the daily consumption of 100 g (~3.5 ounces) of almonds for four weeks led to a 4.9% reduction in non-HDL-cholesterol (i.e., total cholesterol minus HDL-cholesterol) concentration (16).

Blood pressure: Adherence to a Mediterranean diet for nearly four years in the PREDIMED trial led to significant improvements in diastolic (but not systolic) blood pressure compared to a control diet. However, there were no differences in blood pressure changes whether the Mediterranean diet was supplemented with nuts or olive oil (17). A meta-analysis of 21 randomized controlled trials in 1,652 participants found little evidence for an effect of nut supplementation on either systolic or diastolic blood pressure. A blood pressure-lowering effect of nuts was reported when only subjects without type 2 diabetes mellitus were considered. Of note, this meta-analysis included four trials that used either peanuts or soy nuts, which are not tree nuts (18).

Endothelial function: Measures of brachial flow-mediated dilation (FMD), a surrogate marker of endothelial function, are inversely associated with risk of cardiovascular events. A 2017 meta-analysis of eight randomized controlled trials suggested that supplementation with walnuts (four studies), pistachios (three studies), or almonds (one study) for up to 12 weeks may help increase FMD in subjects at risk of cardiovascular disease (19). Similar observations were reported in another recent meta-analysis of randomized controlled trials (20).

Chronic low inflammation: A 2016 meta-analysis of 20 small randomized controlled trials conducted primarily in subjects at high risk for cardiovascular disease found no evidence of an effect of nut supplementation for up to 12 weeks (only two studies lasted longer) on markers of inflammation in blood (21). Of note, four of the trials included in this meta-analysis exclusively supplemented participants with either peanuts or soy nuts. Nonetheless, a similar conclusion was reached in another meta-analysis of 25 interventions (19).

Of note, a recent systematic review of meta-analysis corroborated the account of the cardiovascular health benefits of nut consumption presented above (22).

Cardioprotective compounds in nuts

Nuts are energy-dense in particular because of their high fat content; yet, most of their fat is in the form of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). MUFAs and PUFAs are fatty acids that respectively contain one or more carbon-carbon double bonds (C=C) in their chemical structure, as opposed to saturated fatty acids that have none. Tree nuts contain more MUFAs than PUFAs with the exception of walnuts and pine nuts, which have more PUFAs than MUFAs, and Brazil nuts, which contain equivalent amounts of MUFAs and PUFAs (**Table 1**). Walnuts are especially rich in α-linolenic acid (~0.8 g/ounce), an omega-3 fatty acid with cardioprotective properties (see the article on Essential Fatty Acids). Other bioactive compounds, including micronutrients, phytosterols, and fiber, may also contribute to improving the cardiometabolic profile (**Table 1** and **Figure 1**). Some nuts (pecans, pistachios, almonds, and hazelnuts) are a source of flavonoids that may contribute to cardiovascular health (see the article on Flavonoids) (23). For more information on the nutrient content of nuts, search USDA's FoodData Central.

Table 1. Energy, Protein, Fat, Phytosterols, and Fiber in a 1-ounce Serving of Selected Tree Nuts and Peanuts

Nut (1 ounce[a])	Energy (kcal)	Protein (g)	Total fat (g)	MUFA[b] (g)	PUFA[c] (g)	Phytosterols (mg)	Fiber (g)
Almonds	164	6.0	14.2	8.9	3.5	39	**3.5**
Brazil nuts	187	4.1	19.0	6.8	6.9	21	2.1
Cashews	163	5.2	13.1	7.7	2.2	45	0.9
Hazelnuts	178	4.2	17.2	12.9	2.2	31	2.7
Macadamia nuts	**204**	2.2	**21.5**	**16.7**	0.4	33	2.4
Peanuts[d]	161	**7.3**	14.0	6.9	4.4	—	2.4
Peanut butter, smooth[d] (2 tbsp)	191	7.1	16.4	8.3	4.0	—	1.6
Pecans	196	2.6	20.4	11.6	6.1	36	2.7
Pine nuts (pignoli)	191	3.9	19.4	5.3	9.7	43	1.0
Pistachios	159	5.7	12.8	6.6	4.1	**61**	3.0
Walnuts, Black	175	6.8	16.8	4.4	**10.3**	34	1.9

The greatest contributions to energy, protein, fatty acids, phytosterols, and fiber are highlighted in bold.
[a]One serving of nuts ~1 ounce-equivalent (oz-eq) ~28 grams
[b]Monounsaturated fatty acids
[c]Polyunsaturated fatty acids
[d]Peanuts are legumes, related to beans, lentils, soybeans, and dried peas, yet they are nutritionally similar to tree nuts.

The US Food and Drug Administration (FDA) has acknowledged the current evidence for a relationship between nut consumption and cardiovascular disease by approving the following qualified health claim for nuts (24): "Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts (such as macadamia nuts (25)) as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease" (24).

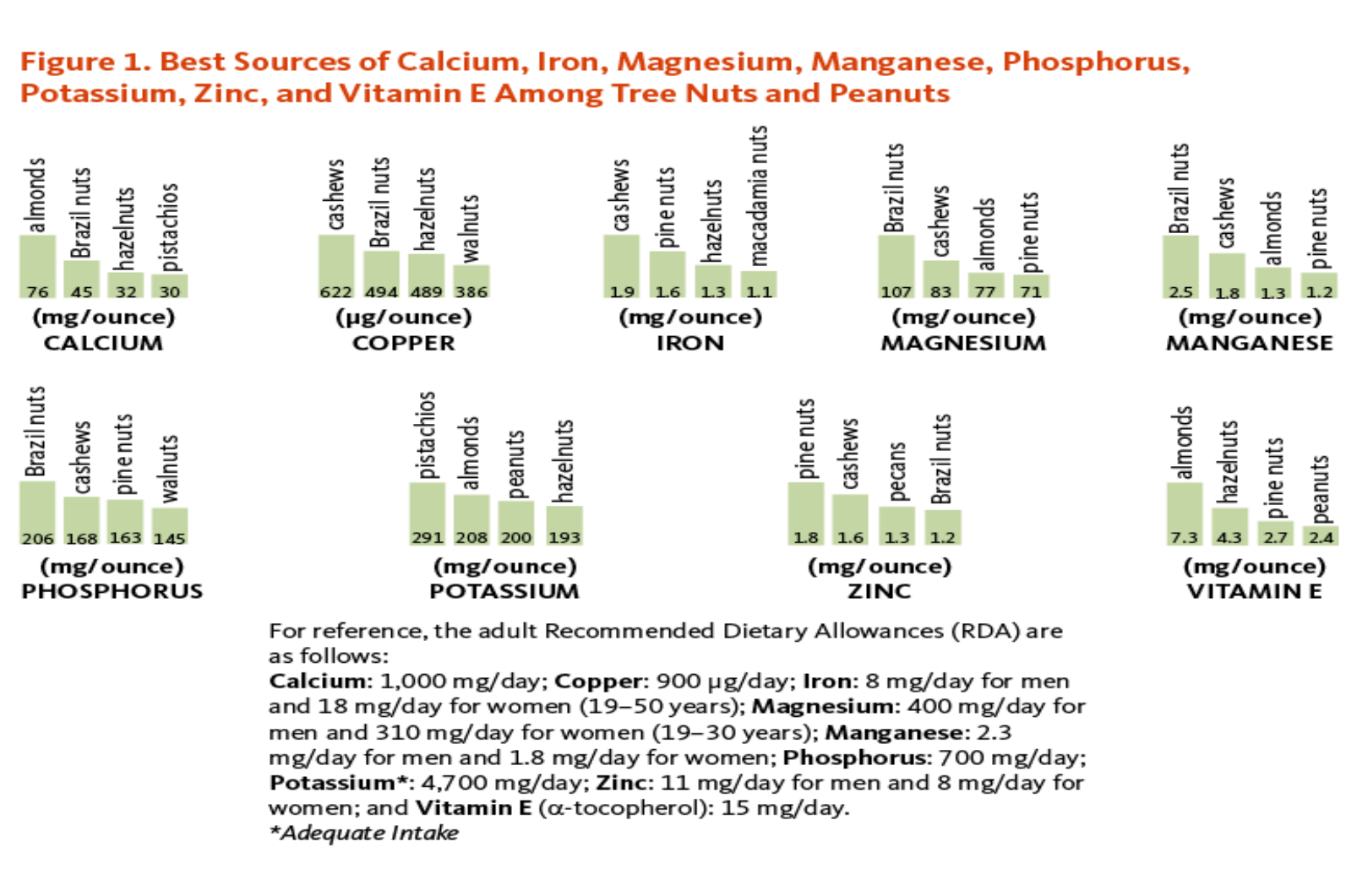
Figure 1. Best Sources of Calcium, Iron, Magnesium, Manganese, Phosphorus, Potassium, Zinc, and Vitamin E Among Tree Nuts and Peanuts

For reference, the adult Recommended Dietary Allowances (RDA) are as follows:
Calcium: 1,000 mg/day; **Copper**: 900 µg/day; **Iron**: 8 mg/day for men and 18 mg/day for women (19–50 years); **Magnesium**: 400 mg/day for men and 310 mg/day for women (19–30 years); **Manganese**: 2.3 mg/day for men and 1.8 mg/day for women; **Phosphorus**: 700 mg/day; **Potassium***: 4,700 mg/day; **Zinc**: 11 mg/day for men and 8 mg/day for women; and **Vitamin E** (α-tocopherol): 15 mg/day.
**Adequate Intake*

[Figure 1 - Click to Enlarge]

Type 2 diabetes mellitus

Early results from the Nurses' Health Study I suggested that nut and peanut butter consumption might be inversely associated with the risk of type 2 diabetes mellitus in women (26). However, two independent meta-analyses of more recent prospective cohort reported no evidence of an association between nut consumption and risk of type 2 diabetes (27, 28).

Nonetheless, a meta-analysis of 12 randomized controlled trials in 450 participants with type 2 diabetes showed that supplementation with tree nuts for a median of eight weeks could reduce fasting glucose concentration and glycated hemoglobin (HbA1c) concentration, a measure of glycemic control (29). Although there were no significant effects on fasting insulin concentration or a measure of insulin resistance (HOMA-IR) (29), these findings suggest that nuts might be part of a healthful diet for the management of hyperglycemia in individuals with type 2 diabetes.

Weight control

A frequent concern is that increased consumption of nuts, which are high in fatty acids and energy dense, may cause weight gain and obesity. A data analysis of NHANES 2005-2010 found that tree-nut consumers (≥¼ ounce/day) had significantly lower BMI and waist circumference than non-consumers (<¼ ounce/day) and were 23% less likely of becoming overweight or obese (9). In addition, in the European Prospective Investigation into Cancer and Nutrition study (EPIC-PANACEA) that followed 373,293 adults (ages, 25-70 years), weight gain over a five-year period was significantly lower (-0.07 kg) in those in the highest quartile of nut intake (median, 12.4 g/day) compared to non-consumers (30). Moreover, the risk of becoming overweight or obese was also 5% lower in those in the highest quartile of nut intake compared to non-consumers (30). A 2013 meta-analysis of small randomized controlled trials found that changes in measures of body weight (28 trials, 1,806 participants), BMI (14 trials, 1,057 participants), or waist circumference (5 trials, 681 participants) were similar when nut-rich diets were compared to standard diets (31). There was some weak evidence suggesting modest reductions in body weight, BMI, and waist circumference measures with nut-rich diets (compared to standard diets) in energy-restriction rather than weight-maintenance interventions (31).

Current epidemiological data indicate that higher nut consumption does not result in greater weight gain; rather, incorporating nuts into diets may be beneficial for weight control.

Finally, it has been suggested that higher amounts of protein and fiber in nuts could enhance satiety and suppress hunger (32). In a recent randomized controlled trial in 100 overweight or obese participants, weight loss and improvements in blood lipid profile and blood pressure over a six-month period were found to be similar regardless of whether walnuts were supplemented to a reduced-energy density diet (33). In addition, there was no difference in reports of satiety between groups (33).

Cancer

Only a few observational studies have examined nut intake in relation to cancer risk. In the Netherlands Cohort Study that followed 120,852 adults (ages, 55-69 years) for about 20 years, there was no association between tree nut, peanut, peanut butter, and total nut consumption and the risk of pancreatic cancer (34). Another analysis of data from 62,573 women in this cohort showed that the highest versus lowest quartile of total nut intake (≥10 g/day versus 0 g/day) was associated with a 45% reduced risk of certain breast cancer subtypes, namely ER- and ER-/PR- (estrogen receptor-negative/progesterone receptor-negative) breast cancers (35). Nut intakes were not associated with other breast cancer subtypes or total breast cancer (35). In a recent analysis of the NIH-AARP Diet and Health Study that followed 566,407 men and women (ages, 50-71 years) for a median 15.5 years, the highest versus lowest quartile (median, 2.20 g/1,000 kcal versus 0 g/1,000 kcal) of total nut intakes (walnuts, peanuts, seeds, and other nuts) was associated with a 27% lower risk of gastric noncardia adenocarcinoma (36). There were no associations between total nut intake and risk of gastric cardia adenocarcinoma, esophageal adenocarcinoma, or esophageal squamous cell carcinoma (36). Although nuts contain many anti-carcinogenic compounds, including some vitamins, minerals, unsaturated fatty acids, phytosterols, and fiber, there is very little evidence that nut consumption might protect against cancer.

Cognitive function

An analysis of NHANES data from the 1988-1994 and 1999-2002 surveys suggested higher scores on cognitive tests in participants (ages ≥20 years) with regular intakes of walnuts (>10 g/day) compared to non-consumers (37). In the Nurses' Health Study I, which included 19,415 women ≥70 years of age, the highest quintile of long-term nut intake (≥5 servings/week) was associated with higher scores on global cognition and verbal memory tests compared to the lowest quintile of intake (<1 serving/month) (38). However, total nut intake in this study was not linked to rate of cognitive decline among individuals over a six year-period (38). Results from the PREDIMED study in 522 participants (mean age, 74.6 years) at high vascular risk showed higher global cognition test scores in those assigned to a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts compared to those fed a control diet for 6.5 years (39). Although participants in each intervention group were unlikely to be cognitively different as a result of randomization at the start of the study, baseline cognitive status was not assessed and thus the conclusions of this study are limited (39). A follow-up PREDIMED study in 334 older adults (mean age, 66.8 years) whose cognitive functions have been assessed both at enrollment and at study completion showed little-to-no evidence of differences in changes in individual test scores over four years between intervention groups and the control group (40). However, when composite test scores were considered to better describe cognitive functions, the result showed that the consumption of a diet supplemented with either extra-virgin olive oil or mixed nuts prevented the decline of global cognitive function, as well as verbal and episodic memory and frontal cognitive functions (attention, cognitive flexibility, and working memory), which was reported in the subjects randomized to the control diet.

Mortality

A meta-analysis of 15 prospective cohort studies, including 819,448 participants, found a 19% lower mortality risk with the highest versus lowest levels of total nut intake (41). Intakes of tree nuts (four studies), peanuts (five studies), and peanut butter (two studies), separately, were also inversely associated with mortality. In addition, there was a non-linear dose-response relationship between total nut intake and mortality, suggesting a greater benefit of increasing intakes when intakes are initially low and no additional protection with intakes beyond 15 to 20 g/day. Higher intakes of total nuts were also found to be inversely associated with mortality related to respiratory disease (three studies) and diabetes mellitus (four studies) (41). These results corroborated findings from other recent meta-analyses (27, 42, 43).

It has been hypothesized that nut consumption could reduce the risk of disease and prolong life through influencing the length of telomeres that protect the ends of chromosomes. Bioactive compounds in nuts might regulate oxidative stress and inflammation, which are important drivers of telomere shortening, a marker of biological aging. A few cross-sectional studies have examined the associations between nut consumption and leukocyte telomere length, yet the findings have been rather inconsistent (44-47).

Safety

Nut allergies

Peanuts and tree nuts are among the most common foods to trigger allergic reactions, potentially severe (anaphylaxis) and fatal (48). Such reactions can be triggered by a primary antibody response against some nut proteins or by antibodies raised against protein in pollen but cross-reacting with structurally similar proteins in nuts. Mixed method-based estimates of peanut allergy in US children suggest that the condition is increasingly prevalent and ranges between 2 and 5% (49). Estimates based solely on self reports suggest a prevalence of tree nut allergy <1% in US adults and <2% in US children (50). Individuals with peanut or tree nut allergies need to take special precautions to avoid inadvertently consuming peanuts or tree nuts by checking labels and avoiding unlabeled snacks, candies, and desserts (50). See the Food Allergy Research and Education website for additional tips to avoiding unintentional peanut or tree nut exposure.

Nut consumption during pregnancy and lactation

In the 2010 'Guidelines for the Diagnosis and Management of Food Allergy in the United States,' the National Institute of Allergy and Infectious Diseases discourages nut avoidance during pregnancy or breastfeeding as a way of preventing food intolerance in the offspring (51). Results from two birth cohort studies suggested an inverse association between maternal peanut or tree nut consumption during, shortly before, or just after their pregnancy and the risk of food allergy (including nut allergy) in the offspring (52, 53), supporting the current recommendations. Yet, prior studies found higher peanut consumption in mothers of children with peanut allergy (54). Additional studies are needed to clarify the effect of maternal nut intake on food tolerance in the offspring.

Introduction to peanuts during infancy

A 2017 addendum to the 2010 'Guidelines for the Diagnosis and Management of Food Allergy in the United States' included recommendations for the prevention of peanut allergy through the early introduction of peanuts in infants' diet (55) (**Table 2**).

Table 2. 2017 Recommendations for the Introduction of Age-appropriate Peanut-containing Foods for Peanut Allergy Prevention (55)

Infant Criteria	Earliest Age for Peanut Introduction	Recommendations
Severe eczema and/or egg allergy	4-6 months	• Peanut introduction only after measurement of peanut-specific antibodies and/or skin prick testing are found negative. • Peanut introduction should start after the introduction of solid foods without peanuts. • Infant may still benefit from early peanut introduction even if the 4-6 month window is missed.
Mild-to-moderate eczema	~6 months	• Introduce peanut-containing foods.
No eczema or food allergies	Age-appropriate and in accordance with family preferences	• Introduce peanut-containing foods.

Adverse effects

Brazil nuts grown in areas of Brazil with selenium-rich soil may provide more than 100 μg of selenium in one nut, while those grown in selenium-poor soil may provide 10 times less (56). For information regarding toxicity of selenium, see the article on Selenium.

Intake Recommendations

Regular nut consumption, equivalent to 1 ounce of nuts five times weekly, has been consistently associated with significant reductions in risk of coronary heart disease in epidemiological studies. Consuming nuts daily as part of a diet that is low in saturated fat has been found to lower serum total and LDL-cholesterol in a number of controlled clinical trials. Since an ounce of most nuts provides at least 160 calories (kcal), simply adding an ounce of nuts daily to one's habitual diet without eliminating other foods may result in weight gain. Substituting unsalted nuts for less healthy snacks or for meat in main dishes are two ways to make nuts part of a healthful diet. A modeling study that used 2009-2012 NHANES data from 17,444 individuals (≥1 year old) estimated that substituting tree nuts for between-meal snacks on a calorie-per-calorie basis would improve the nutritional quality of dietary intakes through a shift in fatty acid intake (less saturated and more unsaturated fatty acids), a reduction in added sugar and sodium (salt), and an increase in potassium, magnesium, and fiber (57).

The 2015-2020 Dietary Guidelines for Americans encourage the consumption of nuts, seeds, and soy products as part of a healthy diet. The recommendations are presented in **Table 3**.

Table 3. 2015-2020 Dietary Guidelines for Americans: Recommendations[a] for Nuts, Seeds, and Soy Products

Life Stage	Age	Mediterranean-style or US-style Eating Patterns[c]	Vegetarian Eating Pattern[d]
Children	2-3 years	2-3	2-3
Children	4-8 years	2-4	2-7
Children	9-13 years	4-5	5-9
Adolescents	14-18 years	4-6	6-13
Adults	19 years and older	5-6	7-10

[a]Dietary guidelines apply when no quantitative Dietary Reference Intake (DRI) value is available.
[b]The recommendations in ounce-equivalent (oz-eq) per week are based on estimated energy needs that vary with age and gender (see Appendix 2: Estimated Calorie Needs per Day, by Age, Sex, and Physical Activity Level). Recommended weekly intakes of nuts, seeds, and soy products, at all calorie requirement levels can be found in the '2015-2020 Dietary Guidelines for Americans' report.
[c]Recommended amounts for nuts, seeds, and soy products.
[d]Recommended amounts for nuts and seeds. Separate recommendations are made for soy products.

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Whole Grains

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Summary

- Grains are the edible seeds of specific grasses of the Poaceae family and include wheat, rice, maize (corn), barley, oats, rye, triticale, millet, bulgur, and sorghum. Quinoa, amaranth, and buckwheat are pseudo-grains that are nutritionally similar to true grains. *(More information)*
- Whole grains are defined as intact or cracked, crushed, and flaked grain seeds in which all the components of the kernel, i.e., the bran, the endosperm, and the germ, are retained in the same relative proportions as in the intact grain. *(More information)*

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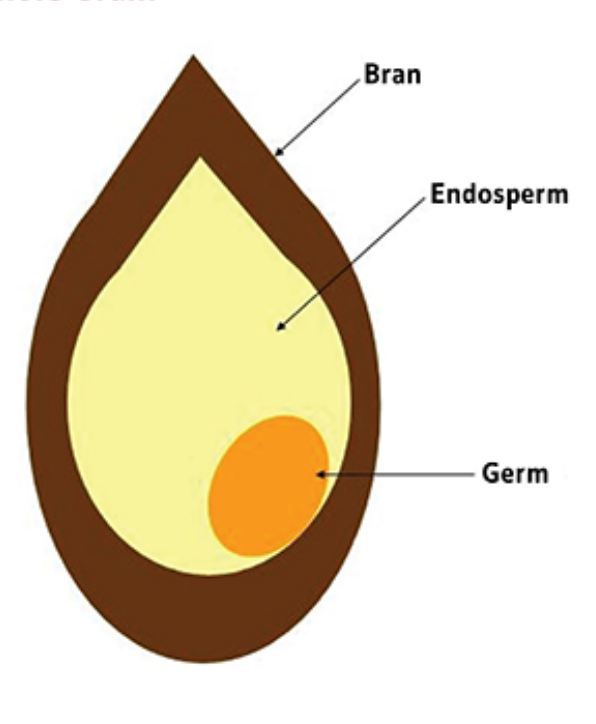
- endosperm, and the germ, are retained in the same relative proportions as in the intact grain. (More information)
- Bran and germ, which are lost during the refining (milling) process, are rich in minerals, vitamins, phytochemicals, and dietary fiber that play important roles in the health benefits associated with whole-grain consumption. *(More information)*
- There is no consensus as to what constitutes a whole-grain food. Products that bear the FDA health claims for whole grains contain at least 51% of whole-grain ingredients by weight. *(More information)*
- Observational studies have found that diets rich in whole grains are associated with reduced risks of type 2 diabetes mellitus and cardiovascular disease compared to diets high in refined grains. *(More information)*
- Although the protective effects of whole grains against cancer are not as well established as those against cardiovascular disease and type 2 diabetes mellitus, some prospective cohort studies have found whole-grain intake to be associated with a decreased risk of esophageal and colorectal cancers. *(More information)*
- Results from large prospective cohort studies showed that whole-grain consumption was inversely correlated with all-cause mortality and mortality from several conditions, including cardiovascular disease, cancer, type 2 diabetes mellitus, respiratory disease, and infections. *(More information)*
- Diets rich in whole grains and fiber may help prevent constipation in healthy people and the formation of pouches (diverticula) in the wall of the colon. In a recent prospective cohort study, higher intakes of dietary fiber, especially from cereal and fruit, was associated with a significantly lower risk of diverticular disease. *(More information)*
- The 2015-2020 Dietary Guidelines for Americans recommend consuming a minimum of three servings (about 90 g) of whole-grain products daily. *(More information)*

Introduction

Grains are seeds of plants belonging to the Poaceae family (also called Gramineae or true grasses). Some examples of edible grains include wheat, rice, maize (corn), barley, oats, rye, triticale (wheat-rye hybrid), millet, bulgur, and sorghum (1). Although they are not members of the Poaceae family, whole-grain ingredients also include pseudo-grains like quinoa, amaranth, and buckwheat. A whole grain has an outer layer of bran, a carbohydrate-rich middle layer called the endosperm, and an inner germ layer (**Figure 1**). Whole-grain foods contain entire grain seeds either intact, cracked, crushed, or flaked, as long as the bran, endosperm, and germ are retained in the same proportions as they exist in the intact kernel (1). Whole grains are rich in potentially beneficial compounds, including vitamins, minerals, fiber, and phytochemicals, such as lignans and phytosterols (2). Most of these compounds are located in the bran or the germ of the grain, both of which are lost during the refining (milling) process, leaving only the starchy endosperm (1). Compared to diets high in refined grains, diets rich in whole grains are associated with reduced risks of several chronic diseases. The health benefits of whole grains are not entirely explained by the individual contributions of the nutrients and phytochemicals they contain. Whole grains represent a unique package of energy, micronutrients, and phytochemicals that work synergistically to promote health and prevent disease (3).

Figure 1. Anatomy of a Whole Grain



Disease Prevention

Because there is no globally accepted definition as to what constitutes a whole-grain food, it is difficult to compare studies that examined the effects of whole-grain consumption on markers of health and disease outcomes. The US Food and Drug Administration (FDA) approved health claims for whole grains (see Finding whole grain foods) to foods containing ≥51% of whole-grain ingredients by weight or ≥8 g of whole grains per one ounce (~30 g)-serving size (4). An international multidisciplinary expert group recently proposed to label "whole grain" a food with a whole-grain content of ≥8 g per ounce (5). Yet, to date, most epidemiological studies that examined the health impact of consuming whole-grain foods have included foods containing ≥25% of whole grains and added brans by weight (6).

Type 2 diabetes mellitus

A recent meta-analysis of eight large prospective cohort studies, including 385,868 participants, have found that high versus low intakes of total grains and whole grains were associated with a significant reduction in the risk of developing type 2 diabetes mellitus (7). On the other hand, no relationship was found between refined-grain intake and diabetes in a meta-analysis of six prospective studies of 258,078 subjects (7). Specifically, the consumption of three daily servings of whole-grain foods was associated with a 32% lower risk of diabetes (see below for Examples of one serving of whole grains). Further analyses showed a significantly lower risk of diabetes with high versus low consumption of whole grains as a single food (i.e., brown rice, wheat bran) or as an ingredient in food (i.e., whole-grain bread, whole-grain breakfast cereal) but not with refined grains like white rice and wheat germ (7). In addition, a pooled analysis of three large prospective cohorts — the Health Professionals Follow-up Study [HPFS] and the Nurses' Health Studies [NHS I and II] — reported a 17% increased risk of type 2 diabetes in participants in the highest (≥5 servings/week) versus lowest (<1 serving/month) quintile of white rice intake, while brown rice consumption (≥2 servings/week versus <1 serving/month) was associated with an 11% reduction in risk (8). Interestingly, substituting 50 g/day (⅔ serving/day) of brown rice or other whole grains for the same amount of white rice could be associated with a predicted diabetes risk reduction of 16% or more (8).

Whole grains and glucose control

Whole grains have been hypothesized to reduce the risk of type 2 diabetes mellitus by improving postprandial glycemia. Immediately after a meal, blood glucose and lipid concentrations are increased, and secretion of insulin by the pancreas stimulates glucose and lipid storage into tissues. Prolonged postprandial hyperglycemia and hyperlipidemia have been associated with oxidative stress, inflammation, insulin resistance, and endothelial dysfunction, all contributing to the development of chronic diseases like type 2 diabetes mellitus (9). The refining process that removes bran and germ facilitates the digestion of the carbohydrate-rich endosperm such that carbohydrates from refined grains were thought to elicit a higher and more rapid elevation in blood glucose, as well as a greater demand for insulin, than whole grains (10). However, compared with foods made from refined grains, whole-grain products do not necessarily have a lower glucose-raising potential, i.e., a lower glycemic index (GI) (11). The GI concept is based on the idea that foods containing carbohydrates that are easily digested, absorbed, and metabolized have a high GI (GI ≥70 on the glucose scale); in contrast, foods containing slowly digestible carbohydrates that elicit a reduced postprandial glucose response are considered to have a low GI (GI ≤55 on the glucose scale) (see also the article on Glycemic Index and Glycemic Load) (12). Bread, breakfast cereal, rice, and snack products have been attributed either a low or high GI, whether or not they include whole grains (11), suggesting that the type of food rather than its whole-grain content affects postprandial blood glucose concentrations.

In some observational studies, higher whole-grain intakes have been associated with decreased insulin resistance (13) and increased insulin sensitivity (14) in healthy individuals. In a controlled cross-over trial in 11 overweight or obese adults, consumption of a diet rich in whole grains for six weeks lowered several clinical measures of insulin resistance compared with a diet high in refined grains (15). However, in a recent randomized controlled study of 61 adults with metabolic syndrome, the consumption of a diet based on several whole-grain cereal products for 12 weeks had no effect on fasting plasma concentrations of glucose, insulin, lipids, or on insulin resistance compared with a refined grain-based diet. Yet, postprandial plasma insulin and triglycerides — but not postprandial plasma glucose — were significantly reduced with the whole grain-based diet (16). A decreased postprandial insulin response may be associated with an increase in tissue sensitivity to insulin (3). In another intervention trial in 20 healthy volunteers, three-day consumption of whole barley-based bread induced a lower insulin peak value following a standard breakfast than the same course with refined wheat bread. Whole barley-based bread consumption was also associated with an increase in circulating concentrations of gut-related hormones (e.g., peptide YY, glucagon-like peptide) and a higher gut fermentation activity. This suggested improvements in hormonal control of digestion and in colonic fermentation of resistant starch (indigestible fiber) (17), possibly promoting the feeling of satiety (18) and increasing insulin sensitivity (19).

Whole-grain consumption might be improving insulin sensitivity rather than blunting postprandial hyperglycemia; however, well-designed, large randomized controlled trials are necessary to provide further insight into how whole-grain consumption may protect against type 2 diabetes.

Cardiovascular disease

A meta-analysis of 10 large prospective cohort studies published between 1998 and 2010 found that the highest intake of whole grains (about three servings daily) was associated with an overall 21% reduced risk of cardiovascular disease (CVD), including coronary heart disease (CHD), ischemic heart disease, heart failure, and ischemic stroke, when compared to the lowest intake of whole grains and after adjustment for several CVD risk factors (20). Further, although evidence is currently limited, whole-grain intake may be associated with a reduced risk of hypertension, a risk factor for cardiovascular disease (21, 22).

Compared to refined grains, whole grains are rich in nutrients associated with cardiovascular risk reduction. In the Health Professionals Follow-up Study (HPFS) in 42,850 men, the top versus bottom quintile (49.6 g/day vs. 3.3 g/day) of whole-grain intake was associated with a 16% reduced risk of CHD after multiple adjustments for age, gender, and CHD risk factors (23). Further adjustments for whole-grain constituents, such as fiber, folate, magnesium, manganese, vitamin B_6 and vitamin E, attenuated the association such that it was no longer statistically significant, suggesting that the micronutrient and fiber content may explain the cardiovascular benefits of consuming whole grains. Protective cardiovascular effects associated with higher intakes of whole grains and lower intakes of refined grains have included improvements in blood lipid profiles and reductions in markers of subclinical inflammation.

Whole grains and cardiometabolic markers

A meta-analysis of 21 randomized controlled trials indicated that whole-grain interventions for 4 to 16 weeks could improve an individual's blood concentrations of fasting glucose, insulin, total and LDL-cholesterol, as well as reduce diastolic and systolic blood pressure (20). Consistent with this, a recently updated meta-analysis of 23 randomized controlled trials published between 1988 and 2015 indicated that consumption of whole grains (28 g/day-213 g/day for 2 to 16 weeks), especially whole-grain oats in cereal and other products, for a couple of weeks resulted in significant reductions in blood concentrations of triglycerides and total and LDL-cholesterol when compared to control diets with refined grain (24). Interventions that included mixed whole-grain products (bread, muesli, ready-to-eat cereal, pasta, rice, crisps, muffins, cookies) also improved blood HDL-cholesterol concentrations (24). In addition, although wheat fiber has not been found to lower serum cholesterol concentrations, numerous clinical studies have demonstrated that increasing intakes of oat fiber and soluble fiber from barley resulted in modest reductions in total and LDL-cholesterol (25-27). In light of such findings, the US Food and Drug Administration (FDA) approved claims regarding whole grains and reduction in risk of CHD that apply to diets low in saturated fat and cholesterol providing at least 3 g/day of β-glucan soluble fiber from oats (oat bran, rolled oats [oatmeal], whole oat flour) or whole-grain barley (28). Whole grains are also sources of phytosterols — compounds that can decrease serum cholesterol by interfering with its intestinal absorption (2).

Whole grains and inflammation markers

Evidence from observational studies suggested an inverse association between whole-grain intake and chronic low-grade inflammation that characterizes cardiovascular and metabolic diseases (29). However, intervention studies have provided mixed results. In a recent cross-over trial in healthy low whole-grain consumers, the effect of increased consumption of mixed whole grains (mean intake, 168 g/day) for six weeks was compared to whole-grain consumption of less than 16 g/day. Increasing whole-grain intake had no effect on absolute counts of immune cells in blood (leukocytes, lymphocytes, natural killer cells), on *ex vivo* phagocytic activities of these cells, or on markers of inflammation (e.g., IL-10, TNF-α, C-reactive protein [CRP]) in blood (30). Previous randomized controlled studies in healthy normal weight, overweight, or obese subjects have also failed to demonstrate any benefits of whole-grain intake on markers of inflammation (31-35). One eight-week dietary intervention study in 80 overweight or obese subjects found that replacement of refined products in the habitual diet by whole-grain wheat products resulted in a significant reduction in pro-inflammatory cytokine TNF-α, a transient increase in anti-inflammatory IL-10, and no change in CRP compared to intake of refined wheat (36). In another randomized cross-over intervention study, overweight/obese children (ages, 8-15 years) were provided with a list of whole-grain products and asked to either obtain half of their grain servings from whole-grain foods every day for six weeks (whole-grain group) or abstain from consuming any of these foods (control group). Mean daily consumption of 98 g of whole-grain products (compared to 11 g/day) resulted in reductions in serum concentrations of CRP, sICAM-1 (soluble intercellular adhesion molecule-1), acute phase protein SAA (serum amyloid A), and leptin (37). An increased whole-grain intake to about five daily servings (compared to <1 serving/day) also reduced blood concentrations of CRP but had no effect on IL-10 and TNF-α concentrations in obese adults with metabolic syndrome following a hypocaloric diet (38). Inconsistency among studies may be attributed to differences in the health status of participants, the duration of interventions, and/or the types of whole grains selected. In particular, if foods with a low glycemic index (GI) can lower cardiometabolic and inflammation markers (39), substituting refined grain products by whole grains with high GI may not demonstrate any benefits regarding the risk of heart disease.

Cancer

Although the protective effects of whole grains against various types of cancer are not as well established as those against type 2 diabetes mellitus and cardiovascular disease, numerous case-control studies have found inverse associations between whole-grain intake and cancer risk (40-42). An early meta-analysis of 40 case-control studies examining 20 different types of cancer found that people with higher whole-grain intakes had an overall risk of cancer that was 34% lower than those with lesser whole-grain intakes (40). Higher intakes of whole grains were most consistently associated with decreased risk of gastrointestinal tract cancers, including cancers of the mouth, throat, esophagus, stomach, colon, and rectum. A prospective cohort study that followed more than 61,000 Swedish women for 15 years found that those who consumed more than 4.5 servings of whole grains daily had a 35% lower risk of colon cancer than those who consumed less than 1.5 servings of whole grains daily (43). In the large National Institutes of Health (NIH)-AARP Diet and Health prospective study in 291,988 men and 197,623 women, mean whole-grain intakes — much lower than in the above-mentioned Swedish cohort — were also inversely associated with risk of colorectal cancer, especially rectal cancer (44). Specifically, the highest versus lowest quintile of whole-grain intake (2.6 servings/day vs. 0.4 servings/day) was associated with a 36% lower risk of developing rectal cancer (44). In a nested case-control study, including participants of the multicenter European Prospective Investigation into Cancer and Nutrition (EPIC), the top versus bottom quartile of plasma alkylresorcinol concentrations, used as a surrogate marker of whole-grain wheat and rye intakes, was found to be associated with a 52% lower incidence of distal colon cancer. No correlations were reported with the incidence of rectal cancer, colon cancer, and proximal colon cancer, or with the overall incidence of colorectal cancers (45). Not all cohort studies have suggested that whole grains might protect against intestinal cancers (46, 47). However, a dose-response analysis based on the results of six cohort studies found a 17% reduction in colorectal cancer risk with an increment of three servings (three oz-eq or 90 g) of whole grains daily (48). Of note, a recent analysis of three Scandinavian cohorts that are also part of the EPIC study and include over 110,000 participants showed an inverse correlation between total whole-grain intake and esophageal cancer risk. Each 10 g-increase in whole-grain wheat intake was found to be associated with a 50% lower risk of esophageal cancer. Such an association was not observed with whole-grain rye or with whole-grain oats (49).

In contrast to refined-grain products, whole grains are rich in numerous compounds that may be protective against cancer, particularly cancers of the gastrointestinal tract (50). Whole grains are a major source of fiber, and high-fiber intakes are thought to speed up the passage of stool through the colon, allowing less time for potentially carcinogenic compounds to stay in contact with cells that line the inner surface of the colon (51). Dietary fiber can also exert chemopreventive effects via short-chain fatty acids that are generated when fiber is fermented by the colonic microbiota (52). Whole grains also contain compounds such as phenolic acids, lignans, phytoestrogens, flavonoids, and vitamin E, that may modify signal transduction pathways that promote the development of cancer or bind potentially damaging free metal ions in the gastrointestinal tract (53, 54).

Mortality

Recent large prospective cohort studies have investigated the relationship between whole-grain consumption and the risk of all-cause and cause-specific mortality. Higher versus lower intakes of whole grains (1.20 oz-eq/day versus 0.13 oz-eq/day) have been associated with a 17% lower risk of all-cause mortality in the NIH-AARP Diet and Health Study of 367,442 older adults (55). Higher whole-grain intakes were significantly associated with a decreased risk of mortality from cardiovascular disease (-17%), cancer (-15%), type 2 diabetes mellitus (-48%), respiratory disease (-11%), and infections (-23%). These associations were largely attenuated after adjustments for cereal fiber intakes, suggesting a major role for fiber in the protective effects of whole grains on mortality (55). Another recent analysis of two US prospective cohort studies, the Nurses' Health Study (NHS) in 74,341 women and the Health Professionals Follow-up Study (HPFS) in 43,744 men, reported a 9% lower risk of all-cause mortality in individuals in the highest versus lowest quintile of whole-grain intake (56). Higher whole-grain consumption was associated with a 15% lower risk of cardiovascular disease-related mortality, but no correlation was found with cancer-related mortality. Finally, the association of whole-grain intake with mortality was also examined in over 110,000 participants of the Scandinavian HELGA cohort (57). In this cohort, a doubling of the consumption of whole-grain products or that of specific whole-grain wheat, rye, or oats was associated with a reduced risk of all-cause and cause-specific mortality.

These results from cohort studies in the US and northern Europe consistently suggested a role of whole-grain consumption in the prevention of early death.

Intestinal health

Diets rich in whole grains and fiber may help prevent or improve constipation symptoms by softening and adding bulk to stool and by speeding its passage through the colon (58, 59). Such diets are also associated with decreased risk of diverticulosis, a condition characterized by the formation of small pouches (diverticula) in the colon. Although most people with diverticulosis experience no symptoms, about 10%-25% may develop pain or inflammation, known as diverticulitis (58). Diverticulitis was virtually unheard of before the practice of milling (refining) flour began in industrialized countries, and the role of a low-fiber diet in the development of diverticular disease is well established (60). If high-fiber diets reduce the risk of diverticular disease (61, 62), then the source of fiber (e.g., from cereal, fruit, vegetables) may be important. Interestingly, a 5 g-increase in intake of fiber from cereal was found to be associated with a 14% reduced risk of diverticular disease in a UK-based cohort of 690,075 women (mean age, 60 years) followed for up to six years; the risk of diverticular disease was decreased by 15% and 5% with a 5 g-increase in the consumption of fruit fiber and vegetable fiber, respectively (62). High-fiber diets are also recommended for people with diverticulosis in order to prevent the formation of additional diverticula rather than to resolve formed diverticula (58). People with diverticulosis are sometimes advised to avoid eating small seeds and husks to prevent them from becoming lodged in diverticula and causing diverticulitis, especially if they do not consume a high-fiber diet (58). However, it should be noted that no study has ever shown that avoiding seeds or popcorn reduces the risk of diverticulitis in an individual with diverticulosis (60).

Body weight management

Prospective cohort studies have consistently suggested that whole-grain consumption is associated with lower body mass index (BMI) and lower risks of weight gain and obesity (6, 20). However, a recent meta-analysis of randomized controlled trials published between 1988 and 2012 reported no significant effects of whole-grain intakes (from 18.2 g/day-150 g/day for 2 to 16 weeks) on body weight (26 trials), body fat (7 studies), and waist circumference (9 studies) in up to 2,060 normal-weight or overweight/obese adults without chronic health conditions (63). In a recent randomized, open-label, controlled trial in 60 overweight/obese individuals with metabolic syndrome, the consumption of whole grains (about 6-12 servings/day) was compared to that of refined grains during a 12-week intervention period that included a weight-maintenance diet for the first six weeks followed by six weeks of a hypocaloric diet (64). Increased whole-grain intake failed to lower body weight, BMI, percentage of body fat, or waist circumference beyond reductions also observed with consumption of refined grains. Of note, individuals who consumed whole grains showed an improved fasting glycemia compared to those fed refined grains, but other cardiometabolic variables remained unchanged (64). These results contrast with other energy-restricted dietary interventions showing a more favorable effect of whole grains on percentage of body fat compared to refined grains (38, 65). Further investigation is warranted to clarify whether whole-grain consumption could play a role in body weight regulation.

Intake Recommendations

Whole-grain intakes approaching three servings daily are associated with significant reductions in chronic disease risk in populations with relatively low whole-grain intakes. The 2015-2020 Dietary Guidelines for Americans — issued jointly by the US Department of Health and Human Services and US Department of Agriculture — recommend that at least half of all grains consumed be whole grains and to increase whole-grain intake by replacing refined grains with whole grains (66). In the 2015-2020 Dietary Guidelines for Americans, the unit of measure of a whole-grain serving size is the ounce-equivalent (oz-eq). A whole-grain serving size corresponds to (1) one ounce (~30 g) of a 100% whole-grain food in its ready-to-eat form, (2) two ounces of partly whole-grain products, or (3) the amount of food containing 16 g of whole-grain ingredients (67). **Table 1** summarizes the 2015-2020 US Dietary Guidelines for whole-grain intakes.

Table 1. 2015-2020 US Dietary Guideline Recommendations[1,2] for Whole-grain Intakes (according to 66)

Life Stage	Age	Daily Intake (oz-eq/day)[3]	Daily Intake (g/day)[4]
Children	2-3 years	1.5-2.5	24-40
Children	4-8 years	2-3	32-48
Children	9-13 years	2.5-4.5	40-72
Adolescents	14-18 years	3-5	48-80
Adults	19 years and older	3-5	48-80

[1] Dietary guidelines apply when no quantitative Dietary Reference Intake (DRI) value is available.
[2] The recommendations are based on estimated energy needs that vary with age and gender. Recommended daily intakes of whole grains at all calorie requirement levels can be found in the '2015-2020 Dietary Guidelines for Americans' report (see Appendix 3: Healthy US-style eating pattern) (66). For example, for 2,000 calories per day, the daily recommendation for whole-grain consumption is at least three ounce-equivalents or more per day (≥3 oz-eq).
[3] For example, one ounce-equivalent of whole grains can correspond to one ounce (~30 g) of a 100% whole-grain food or two ounces of partly whole-grain products.
[4] Daily intake of whole grains based on 100% whole-grain foods containing 16 grams of whole grains per ounce-equivalent (16 g/oz-eq).

The US National Health and Nutrition Examination Survey (NHANES) 2009-2010 reported mean whole-grain intakes of 0.57 oz-eq/day in children and adolescents and 0.82 oz-eq/day in adults (68). Approximately 40% of Americans consume no whole grains, and only 2.9% of children/adolescents and 7.7% of adults consume ≥3 oz-eq/day of whole grains (68). In view of the potential health benefits of increasing whole-grain intake, three daily servings of whole-grain foods should be seen as a minimum amount, and whole-grain foods should be substituted for refined carbohydrates whenever possible.

Examples of one serving of whole grains

- 1 slice of whole-grain bread
- ½ whole-grain English muffin, bagel, or bun
- 1 ounce of ready to eat whole-grain cereal
- ½ cup of oatmeal, brown rice, or whole-wheat pasta (cooked)
- 5-6 whole-grain crackers
- 1 tortilla (6" diameter)
- 1 pancake (5" diameter)

Increasing whole-grain intake

Finding whole-grain foods

Whole-grain foods may contain amaranth, whole-grain barley, brown and wild rice, buckwheat (kasha), millet, oats, popcorn, quinoa, whole rye, triticale, whole wheat (wheat berries) with various wheat species (including common wheat, emmer, spelt, and khorasan) (69). Unfortunately, it is not always clear from the label whether a product is made mostly from whole grains or refined grains. Some strategies to use when shopping for whole-grain foods include:

- Look for products that list whole grain(s) as the first ingredient(s).
- Look for whole-grain products that contain at least 2 grams of fiber per serving, since whole-grain foods are usually rich in fiber.
- Look for products that display the following health claim: "Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol may help reduce the risk of heart disease and certain cancers." Products displaying this health claim must contain at least 51% whole grain by weight or at least 8 grams of whole grains per ounce-equivalent (4).
- Look for whole-wheat pasta that lists whole-wheat flour as the first ingredient. Most pasta is made from refined semolina or durum wheat flour.
- Be aware that foods labeled with words like "multi-grain," "stone-ground," "100% wheat," "seven-grain," "cracked wheat," or "bran" are usually not 100% whole-grain products or can even be completely devoid of any whole grains (1).

Some strategies for increasing whole-grain intake

- Eat whole-grain breakfast cereal, such as wheat flakes, shredded wheat, muesli (rolled oats), and oatmeal. Bran cereal is not actually whole-grain cereal, but the high-fiber content makes it a good breakfast choice.
- Substitute whole-grain bread, rolls, tortillas, and crackers for those made from refined grains.
- Substitute whole-wheat pasta or pasta made from 50% whole wheat and 50% white flour for conventional pastas.
- Substitute brown rice for white rice.
- Add whole-grain barley to soups and stews.
- When baking, substitute whole-wheat flour (100% whole-wheat flour, white whole-wheat flour, or whole-wheat pastry flour) for white or unbleached flour.

Bioactive Components in Whole Grains

Whole grains are a source of numerous biologically active components; some are listed in **Table 2**.

Table 2. Some Potentially Beneficial Compounds in Whole Grains

Macronutrients	Vitamins	Minerals	Phytochemicals
Unsaturated Fats	Folate	Magnesium	Fiber
	Vitamin E	Potassium	Flavonoids
		Selenium	Lignans
			Phytosterols

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Glycemic Index and Glycemic Load

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Summary

- The glycemic index (GI) is a measure of the blood glucose-raising potential of the carbohydrate content of a food compared to a reference food (generally pure glucose). Carbohydrate-containing foods can be classified as high- (≥70), moderate- (56-69), or low-GI (≤55) relative to pure glucose (GI=100). *(More information)*
- Consumption of high-GI foods causes a sharp increase in postprandial blood glucose concentration that declines rapidly, whereas consumption of low-GI foods results in a lower blood glucose concentration that declines gradually. *(More information)*
- The glycemic load (GL) is obtained by multiplying the quality of carbohydrate in a given food (GI) by the amount of carbohydrate in a serving of that food. *(More information)*
- Prospective cohort studies found high-GI or -GL diets to be associated with a higher risk of adverse health outcomes, including type 2 diabetes mellitus and cardiovascular disease. *(More information)*
- Meta-analyses of observational studies have found little-to-no evidence of an association between high dietary GI and GL and risk of cancer. *(More information)*
- Lowering the GL of the diet may be an effective method to improve glycemic control in individuals with type 2 diabetes mellitus. This approach is not currently included in the overall strategy of diabetes management in the US. *(More information)*
- Several dietary intervention studies found that low-GI/GL diets were as effective as conventional, low-fat diets in reducing body weight. Both types of diets resulted in beneficial effects on metabolic markers associated with the risk of type 2 diabetes mellitus and cardiovascular disease. *(More information)*
- Lowering dietary GL can be achieved by increasing the consumption of whole grains, nuts, legumes, fruit, and non-starchy vegetables, and decreasing intakes of moderate- and high-GI foods like potatoes, white rice, white bread, and sugary foods. *(More information)*

Glycemic Index

Glycemic index of individual foods

In the past, carbohydrates were classified as simple or complex based on the number of simple sugars in the molecule. Carbohydrates composed of one or two simple sugars like fructose or sucrose (table sugar; a disaccharide composed of one molecule of glucose and one molecule of fructose) were labeled simple, while starchy foods were labeled complex because starch is composed of long chains of the simple sugar, glucose. Advice to eat less simple and more complex carbohydrates (i.e., polysaccharides) was based on the assumption that consuming starchy foods would lead to smaller increases in blood glucose than sugary foods (1). This assumption turned out to be too simplistic since the blood glucose (glycemic) response to complex carbohydrates has been found to vary considerably. The concept of glycemic index (GI) has thus been developed in order to rank dietary carbohydrates based on their overall effect on postprandial blood glucose concentration relative to a referent carbohydrate, generally pure glucose (2). The GI is meant to represent the relative quality of a carbohydrate-containing food. Foods containing carbohydrates that are easily digested, absorbed, and metabolized have a high GI (GI≥70 on the glucose scale), while low-GI foods (GI≤55 on the glucose scale) have slowly digestible carbohydrates that elicit a reduced postprandial glucose response. Intermediate-GI foods have a GI between 56 and 69 (3). The GI of selected carbohydrate-containing foods can be found in **Table 1**.

Measuring the glycemic index of foods

To determine the glycemic index (GI) of a food, healthy volunteers are typically given a test food that provides 50 grams (g) of carbohydrate and a control food (white, wheat bread or pure glucose) that provides the same amount of carbohydrate, on different days (4). Blood samples for the determination of glucose concentrations are taken prior to eating, and at regular intervals for a few hours after eating. The changes in blood glucose concentration over time are plotted as a curve. The GI is calculated as the incremental area under the glucose curve (iAUC) after the test food is eaten, divided by the corresponding iAUC after the control food (pure glucose) is eaten. The value is multiplied by 100 to represent a percentage of the control food (5):

$$\text{GI} = (\text{iAUC}_{\text{test food}}/\text{iAUC}_{\text{glucose}}) \text{ x } 100$$

For example, a boiled white potato has an average GI of 82 relative to glucose and 116 relative to white bread, which means that the blood glucose response to the carbohydrate in a baked potato is 82% of the blood glucose response to the same amount of carbohydrate in pure glucose and 116% of the blood glucose response to the same amount of carbohydrate in white bread. In contrast, cooked brown rice has an average GI of 50 relative to glucose and 69 relative to white bread. In the traditional system of classifying carbohydrates, both brown rice and potato would be classified as complex carbohydrates despite the difference in their effects on blood glucose concentrations.

While the GI should preferably be expressed relative to glucose, other reference foods (e.g., white bread) can be used for practical reasons as long as their preparation has been standardized and they have been calibrated against glucose (2). Additional recommendations have been suggested to improve the reliability of GI values for research, public health, and commercial application purposes (2, 6).

Physiological responses to high- versus low-glycemic index foods

By definition, the consumption of high-GI foods results in higher and more rapid increases in blood glucose concentrations than the consumption of low-GI foods. Rapid increases in blood glucose (resulting in hyperglycemia) are potent signals to the β-cells of the pancreas to increase insulin secretion (7). Over the next few hours, the increase in blood insulin concentration (hyperinsulinemia) induced by the consumption of high-GI foods may cause a sharp decrease in the concentration of glucose in blood (resulting in hypoglycemia). In contrast, the consumption of low-GI foods results in lower but more sustained increases in blood glucose and lower insulin demands on pancreatic β-cells (8).

Glycemic index of a mixed meal or diet

Many observational studies have examined the association between GI and risk of chronic disease, relying on published GI values of individual foods and using the following formula to calculate meal (or diet) GI (9):

$$\text{Meal GI} = [(\text{GI x amount of available carbohydrate})_{\text{Food A}} + (\text{GI x amount of available carbohydrate})_{\text{Food B}} + \ldots]/ \text{ total amount of available carbohydrate}$$

Yet, the use of published GI values of individual foods to estimate the average GI value of a meal or diet may be inappropriate because factors such as food variety, ripeness, processing, and cooking are known to modify GI values. In a study by Dodd et al., the estimation of meal GIs using published GI values of individual foods was overestimated by 22 to 50% compared to direct measures of meal GIs (9).

Besides the GI of individual foods, various food factors are known to influence the postprandial glucose and insulin responses to a carbohydrate-containing mixed diet. A recent cross-over, randomized trial in 14 subjects with type 2 diabetes mellitus examined the acute effects of four types of breakfasts with high- or low-GI and high- or low-fiber content on postprandial glucose concentrations. Plasma glucose was found to be significantly higher following consumption of a high-GI and low-fiber breakfast than following a low-GI and high-fiber breakfast. However, there was no significant difference in postprandial glycemic responses between high-GI and low-GI breakfasts of similar fiber content (10). In this study, meal GI values (derived from published data) failed to correctly predict postprandial glucose response, which appeared to be essentially influenced by the fiber content of meals. Since the amounts and types of carbohydrate, fat, protein, and other dietary factors in a mixed meal modify the glycemic impact of carbohydrate GI values, the GI of a mixed meal calculated using the above-mentioned formula is unlikely to accurately predict the postprandial glucose response to this meal (3). Moreover, the GI is a property of a given food carbohydrate such that it does not take into account individuals' characteristics like ethnicity, metabolic status, or eating habits (e.g., the degree to which we masticate) which might, to a limited extent, also influence the glycemic response to a given carbohydrate-containing meal (11-14).

Using direct measures of meal GIs in future trials — rather than estimates derived from GI tables — would increase the accuracy and predictive value of the GI method (2, 6). In addition, in a recent meta-analysis of 28 studies examining the effect of low- versus high-GI diets on serum lipids, Goff et al. indicated that the mean GI of low-GI diets varied from 21 to 57 across studies, while the mean GI of high-GI diets ranged from 51 to 75 (15). Therefore, a stricter use of GI cutoff values may also be warranted to provide more reliable information about carbohydrate-containing foods.

Glycemic Load

The glycemic index (GI) compares the potential of foods containing the same amount of carbohydrate to raise blood glucose. However, the amount of carbohydrate contained in a food serving also affects blood glucose concentrations and insulin responses. For example, the mean GI of watermelon is 76, which is as high as the GI of a doughnut (see **Table 1**). Yet, one serving of watermelon provides 11 g of available carbohydrate, while a medium doughnut provides 23 g of available carbohydrate.

The concept of glycemic load (GL) was developed by scientists to simultaneously describe the quality (GI) and quantity of carbohydrate in a food serving, meal, or diet. The GL of a single food is calculated by multiplying the GI by the amount of carbohydrate in grams (g) provided by a food serving and then dividing the total by 100 (4):

$$\text{GL}_{\text{Food}} = (\text{GI}_{\text{Food}} \text{ x amount (g) of available carbohydrate}_{\text{Food}} \text{ per serving})/100$$

For a typical serving of a food, GL would be considered high with GL≥20, intermediate with GL of 11-19, and low with GL≤10. Using the above-mentioned example, despite similar GIs, one serving of watermelon has a GL of 8, while a medium-sized doughnut has a GL of 17. Dietary GL is the sum of the GLs for all foods consumed in the diet.

It should be noted that while healthy food choices generally include low-GI foods, this is not always the case. For example, intermediate-to-high-GI foods like parsnip, watermelon, banana, and pineapple, have low-to-intermediate GLs (see **Table 1**).

Disease Prevention

Type 2 diabetes mellitus

The consumption of high-GI and -GL diets for several years might result in higher postprandial blood glucose concentration and excessive insulin secretion. This might contribute to the loss of the insulin-secreting function of pancreatic β-cells and lead to irreversible type 2 diabetes mellitus (16).

A US ecologic study of national data from 1909 to 1997 found that the increased consumption of refined carbohydrates in the form of corn syrup, coupled with the declining intake of dietary fiber, has paralleled the increased prevalence of type 2 diabetes (17). In addition, high-GI and -GL diets have been associated with an increased risk of type 2 diabetes in several large prospective cohort studies. A recent updated analysis of three large US cohorts indicated consumption of foods with the highest versus lowest GI was associated with a risk of developing type 2 diabetes that was increased by 44% in the Nurses' Health Study (NHS) I, 20% in the NHS II, and 30% in the Health Professionals Follow-up Study (HPFS). High-GL diets were associated with an increased risk of type 2 diabetes (+18%) only in the NHS I and in the pooled analysis of the three studies (+10%) (18). Additionally, the consumption of high-GI foods that are low in cereal fiber was associated with a 59% increase in diabetes risk compared to low-GI and high-cereal-fiber foods. High-GL and low-cereal-fiber diets were associated with a 47% increase in risk compared to low-GL and high-cereal-fiber diets. Moreover, obese participants who consumed foods with high-GI or -GL values had a risk of developing type 2 diabetes that was more than 10-fold greater than lean subjects consuming low-GI or -GL diets (18).

However, a number of prospective cohort studies have reported a lack of association between GI or GL and type 2 diabetes (19-24). The use of GI food classification tables based predominantly on Australian and American food products might be a source of GI value misassignment and partly explain null associations reported in many prospective studies of European and Asian cohorts.

Nevertheless, conclusions from several recent meta-analyses of prospective studies (including the above-mentioned studies) suggest that low-GI and -GL diets might have a modest but significant effect in the prevention of type 2 diabetes (18, 25, 26). Organizations like Diabetes UK (27) and the European Association for the Study of Diabetes (28) have included the use of diets of low GI/GL and high in dietary fiber and whole grains in their recommendations for diabetes prevention in high-risk individuals. The use of GI and GL is currently not implemented in US dietary guidelines (29).

Cardiovascular disease

Observational studies

Numerous observational studies have examined the relationship between dietary GI/GL and the incidence of cardiovascular events, especially coronary heart disease (CHD) and stroke. A meta-analysis of 14 prospective cohort studies (229,213 participants; mean follow-up of 11.5 years) found a 13% and 23% increased risk of cardiovascular disease (CVD) with high versus low dietary GI and GL, respectively (30). Three independent meta-analyses of prospective studies also reported that higher GI or GL was associated with increased risk of CHD in women but not in men (31-33). A recent analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) study in 20,275 Greek participants, followed for a median of 10.4 years, showed a significant increase in CHD incidence and mortality with high dietary GL specifically in those with high BMI (≥28 kg/m²) (34). This is in line with earlier findings in the Nurses' Health Study (NHS) showing that a high dietary GL was associated with a doubling of the risk of CHD over 10 years in women with higher (≥23 kg/m²) vs. lower BMI (35). A similar finding was reported in a cohort of middle-aged Dutch women followed for nine years (36).

Additionally, high dietary GL (but not GI) was associated with a 19% increased risk of stroke in pooled analyses of prospective cohort studies (32, 37). A meta-analysis of seven prospective studies (242,132 participants; 3,255 stroke cases) found that dietary GL was associated with an overall 23% increase in risk of stroke and a specific 35% increase in risk of ischemic stroke; GL was not found to be related to hemorrhagic stroke (38).

Overall, observational studies have found that higher glycemic load diets are associated with increased risk of cardiovascular disease, especially in women and in those with higher BMIs.

GI/GL and cardiometabolic markers

The GI/GL of carbohydrate foods may modify cardiometabolic markers associated with CVD risk. A meta-analysis of 27 randomized controlled trials (published between 1991 and 2008) examining the effect of low-GI diets on serum lipid profile reported a significant reduction in total and LDL-cholesterol independent of weight loss (15). Yet, further analysis suggested significant reductions in serum lipids only with the consumption of low-GI diets with high fiber content. In a three-month, randomized controlled study, an increase in the values of flow-mediated dilation (FMD) of the brachial artery, a surrogate marker of vascular health, was observed following the consumption of a low- versus high-GI hypocaloric diet in obese subjects (39).

High dietary GLs have been associated with increased concentrations of markers of systemic inflammation, such as C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α (TNF-α) (40, 41). In a small 12-week dietary intervention study, the consumption of a Mediterranean-style, low-GL diet (without caloric restriction) significantly reduced waist circumference, insulin resistance, systolic blood pressure, as well as plasma fasting insulin, triglycerides, LDL-cholesterol, and TNF-α in women with metabolic syndrome. A reduction in the expression of the gene coding for 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, in blood cells further confirmed an effect for the low-GI diet on cholesterol homeostasis (42). Well-controlled, long-term intervention studies are needed to confirm the potential cardiometabolic benefits of low GI/GL diets in people at risk for CVD.

Cancer

Evidence that high-GI or -GL diets are related to cancer is inconsistent. A recent meta-analysis of 32 case-control studies and 20 prospective cohort studies found modest and nonsignificant increased risks of hormone-related cancers (breast, prostate, ovarian, and endometrial cancers) and digestive tract cancers (esophageal, gastric, pancreas, and liver cancers) with high versus low dietary GI and GL (43). A significant positive association was found only between a high dietary GI and colorectal cancer (43). Yet, earlier meta-analyses of prospective cohort studies failed to find a link between high-GI or -GL diets and colorectal cancer (44-46). Another recent meta-analysis of prospective studies suggested a borderline increase in breast cancer risk with high dietary GI and GL. Adjustment for confounding factors across studies found no modification of menopausal status or BMI on the association (47). Further investigations are needed to verify whether GI and GL are associated with various cancers.

Gallbladder disease

Results of two studies indicate GI and GL may be related to gallbladder disease: a higher dietary GI and GL were associated with significantly increased risks of developing gallstones in a cohort of men participating in the Health Professionals Follow-up Study (48) and in a cohort of women participating in the Nurses' Health Study (49). However, more epidemiological research is needed to determine an association between dietary glycemic index/load and gallbladder disease.

Disease Treatment

Diabetes mellitus

Whether low-GI foods could improve overall blood glucose control in people with type 1 or type 2 diabetes mellitus has been investigated in a number of intervention studies. A meta-analysis of 19 randomized controlled trials that included 840 diabetic patients (191 with type 1 diabetes and 649 with type 2 diabetes) found that consumption of low-GI foods improved short-term and long-term control of blood glucose concentrations, reflected by significant decreases in fructosamine and glycated hemoglobin (HbA1c) levels (50). However, these results need to be cautiously interpreted because of significant heterogeneity among the included studies. The American Diabetes Association has rated poorly the current evidence supporting the substitution of low-GL foods for high-GL foods to improve glycemic control in adults with type 1 or type 2 diabetes (51, 52). Well-controlled studies are needed to further assess whether the use of low-GI/GL diets could significantly improve long-term glycemic control and the quality of life of subjects with diabetes.

A randomized controlled study in 92 pregnant women (20-32 weeks) diagnosed with gestational diabetes found no significant effects of a low-GI diet on maternal metabolic profile (e.g., blood concentrations of glucose, insulin, fructosamine, HbA1c; insulin resistance) and pregnancy outcomes (i.e., maternal weight gain and neonatal anthropometric measures) compared to a conventional high-fiber, moderate-GI diet (53). The low-GI diet consumed during the pregnancy also failed to improve maternal glucose tolerance, insulin sensitivity, and other cardiovascular risk factors, or maternal and infant anthropometric data in a three-month postpartum follow-up study of 55 of the mother-infant pairs (54). In addition, another trial in 139 pregnant women (12-20 weeks' gestation) at high risk for gestational diabetes showed no statistical differences regarding the diagnosis of gestational diabetes during the second and third trimester of pregnancy, the requirement for insulin therapy, and pregnancy outcomes and neonatal anthropometry whether women followed a low-GI diet or a high-fiber, moderate-GI diet (55). At present, there is no evidence that a low-GI diet provides benefits beyond those of a healthy, moderate-GI diet in women at high risk or affected by gestational diabetes.

Obesity

Obesity is often associated with metabolic disorders, such as hyperglycemia, insulin resistance, dyslipidemia, and hypertension, which place individuals at increased risk for type 2 diabetes mellitus, cardiovascular disease, and early death (56, 57). Traditionally, weight-loss strategies have included energy-restricted, low-fat, high-carbohydrate diets with >50% of calories from carbohydrates, ≤30% from fat, and the remainder from protein. However, a recent meta-analysis of randomized controlled intervention studies (≥6 months' duration) has reported that low- or moderate-carbohydrate diets (4%-45% carbohydrate) and low-fat diets (10%-30% fat) were equally effective at reducing body weight and waist circumference in overweight or obese subjects (58).

Low-GI/GL diet versus moderate-GI/GL, low-fat diet

Several dietary intervention studies have examined how low-GI/GL diets compared with conventional low-fat diets to promote weight loss. Lowering the GI of conventional energy-restricted, low-fat diets was proven to be more effective to reduce postpartum body weight and waist and hip circumferences and prevent type 2 diabetes mellitus in women with prior gestational diabetes mellitus (59). In a six-month dietary intervention study in 73 obese adults, no differences in weight loss were reported in subjects following either a low-GL diet (40% carbohydrate and 35% fat) or a low-fat diet (55% carbohydrate and 20% fat). Yet, the consumption of a low-GL diet increased HDL-cholesterol and decreased triglyceride concentrations significantly more than the low-fat diet, but LDL-cholesterol concentration was significantly more reduced with the low-fat than low-GI diet (60).

A one-year randomized controlled study of 202 individuals with a body mass index (BMI) ≥28 and at least another metabolic disorder compared the effect of two dietary counseling-based interventions advocating either for a low-GL diet (30%-35% of calories from low-GI carbohydrates) or a low-fat diet (<30% of calories from fat) (61). Weight loss with each diet was equivalent (~4 kg). Both interventions similarly reduced triglycerides, C-reactive protein (CRP), and fasting insulin, and increased HDL-cholesterol. Yet, the reduction in waist and hip circumferences was greater with the low-fat diet, while blood pressure was significantly more reduced with the low-GL diet (61). In the GLYNDIET study, a six-month randomized dietary intervention trial, the comparison of two moderate-carbohydrate diets (42% of calories from carbohydrates) with different GIs (GI of 34 or GI of 62) and a low-fat diet (30% of calories from fat; GI of 65) on weight loss indicated that the low-GI diet reduced body weight more effectively than the low-fat diet. Additionally, the low-GI diet improved fasting insulin concentration, β-cell function, and insulin resistance better than the low-fat diet. None of the diets modulated hunger or satiety or affected biomarkers of endothelial function or inflammation. Finally, no significant differences were observed in low- compared to high-GL diets regarding weight loss and insulin metabolism (62).

Low-GI/GL diet versus high-GI/GL diet

In a meta-analysis of 14 randomized controlled trials published between 2005 and 2011, neither high- nor low-GI/GL dietary interventions conducted for 6 to 17 months had any significant effect on body weight and waist circumference in a total of 2,344 overweight and obese subjects (63). Low-GI/GL diets were found to significantly reduce C-reactive protein and fasting insulin but had no effect on blood lipid profile, fasting glucose concentration, or HbA1c concentration compared to high-GI/GL diets.

It has been suggested that the consumption of low-GI foods delayed the return of hunger, decreased subsequent food intake, and increased satiety when compared to high-GI foods (64). The effect of isocaloric low- and high-GI test meals on the activity of brain regions controlling appetite and eating behavior was evaluated in a small randomized, blinded, cross-over study in 12 overweight or obese men (65). During the postprandial period, blood glucose and insulin rose higher after the high-GI meal than after the low-GI meal. In addition, in response to the excess insulin secretion, blood glucose dropped below fasting concentrations three to five hours after high-GI meal consumption. Cerebral blood flow was significantly higher four hours after ingestion of the high-GI meal (compared to a low-GI meal) in a specific region of the striatum (right nucleus accumbens) associated with food intake reward and craving. If the data suggested that consuming low- rather than high-GI foods may help restrain overeating and protect against weight gain, this has not yet been confirmed in long-term randomized controlled trials. In the recent multicenter, randomized controlled Diet, Obesity, and Genes (DiOGenes) study in 256 overweight and obese individuals who lost ≥8% of body weight following an eight-week calorie-restricted diet, consumption of *ad libitum* diets with different protein and GI content for 12 months showed that only high-protein diets — regardless of their GI — could mitigate weight regain (66). However, the dietary interventions only achieved a modest difference in GI (~5 units) between high- and low-GI diets such that the effect of GI in weight maintenance remained unknown.

Lifestyle modification programs do not currently include the reduction of calories from carbohydrate as an alternative to standard prescription of low-fat diets, nor do they suggest the use of GI/GL as a guide to healthier dietary choices (67).

Lowering Dietary Glycemic Load

Some strategies for lowering dietary GL include:

- Increasing the consumption of whole grains, nuts, legumes, fruit, and non-starchy vegetables
- Decreasing the consumption of starchy, moderate- and high-GI foods like potatoes, white rice, and white bread
- Decreasing the consumption of sugary foods like cookies, cakes, candy, and soft drinks

Table 1 includes GI and GL values of selected foods relative to pure glucose (68). Foods are ranked in descending order of their GI values, with high-GI foods (GI≥70) at the top and foods with low-GI values (≤55) at the bottom of the table. To look up the GI values for other foods, visit the University of Sydney's GI website.

Table 1. GI and GL Values for Selected Foods

Food	GI (Glucose=100)	Serving Size	Carbohydrate* per Serving (g)	GL per Serving
Russet potato, baked	111	1 medium	30	33
Potato, white, boiled (average)	82	1 medium	30	25
Puffed rice cakes	82	3 cakes	21	17
Cornflakes	79	1 cup	26	20
Jelly beans	78	1 oz	28	22
Doughnut	76	1 medium	23	17
Watermelon	76	1 cup	11	8
Soda crackers	74	4 crackers	17	12
Bread, white-wheat flour	71	1 large slice	14	10
Pancake	67	6" diameter	58	39
Rice, white, boiled	66	1 cup	53	35
Table sugar (sucrose)	63	2 tsp	10	6
Dates, dried	62	2 oz	40	25
Spaghetti, white, boiled (20 min)	58	1 cup	44	25
Honey, pure	58	1 Tbsp	17	10
Pineapple, raw	58	½ cup	19	11
Banana, raw	55	1 cup	24	13
Maple syrup, Canadian	54	1 Tbsp	14	7
Parsnips, peeled, boiled	52	½ cup	10	5
Rice, brown, boiled	50	1 cup	42	20
Spaghetti, white, boiled (average)	46	1 cup	44	20
Whole-grain pumpernickel bread	46	1 large slice	12	5
All-Bran™ cereal	45	1 cup	21	10
Spaghetti, whole-meal, boiled	32	1 cup	37	14
Orange, raw	42	1 medium	11	5

Apple, raw	39	1 medium	15	6
Pear, raw	38	1 medium	11	4
Skim milk	33	8 fl oz	13	4
Carrots, boiled	33	½ cup	4	1
Lentils, dried, boiled	29	1 cup	24	7
Kidney beans, dried, boiled	28	1 cup	29	8
Pearled barley, boiled	28	1 cup	38	11
Cashews	25	1 oz	9	2
Peanuts	18	1 oz	6	1

*Amount of available carbohydrates in a food serving that excludes indigestible carbohydrates, i.e., dietary fiber.

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Coffee

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Summary

- Coffee is a complex mixture of chemicals that provides significant amounts of chlorogenic acid and caffeine. *(More information)*
- Unfiltered coffee is a significant source of diterpenes (mainly cafestol and kahweol) that appear to raise serum total and LDL-cholesterol concentrations in humans. *(More information)*
- The results of observational studies suggest that coffee consumption is associated with lower risks of type 2 diabetes mellitus, Parkinson's disease, liver disease, and mortality. However, it is premature to recommend coffee consumption for disease prevention based on this evidence. *(More information)*
- Coffee consumption has been associated with lower risks of cirrhosis, cirrhosis-related mortality, and liver cancer. Coffee consumption was also found to be inversely associated with the risk of oral/pharyngeal cancer, colon cancer, prostate cancer, endometrial cancer, and melanoma. Evidence also suggests that coffee consumption is not a risk factor for lung cancer. *(More information)*
- Despite evidence from clinical trials that caffeine in coffee can increase blood pressure, most prospective cohort studies have not found moderate coffee consumption to be associated with increased risk of cardiovascular disease. *(More information)*
- Caffeine intake comparable to the amount in 2-3 cups of coffee may raise blood pressure, especially in people with borderline or high blood pressure. However, regular coffee consumption in hypertensive subjects has not been associated with an increased risk of cardiovascular disease. *(More information)*
- Current evidence from dose-response meta-analyses of observational studies does not exclude that moderate maternal coffee consumption could adversely affect fetal growth during pregnancy. Limiting intakes of caffeinated coffee to ≤1 cup/day during pregnancy and 2-3 cups/day during breast-feeding is recommended. *(More information)*
- Ensuring adequate calcium and vitamin D intakes and limiting coffee consumption to 3 cups/day (~300 mg/day of caffeine) are unlikely to cause any adverse effects on calcium absorption and bone health. *(More information)*
- Overall, there is little evidence of health risks and some evidence of health benefits for adults consuming moderate amounts of filtered coffee (3-4 cups/day providing ~300-400 mg/day of caffeine). *(More information)*

Introduction

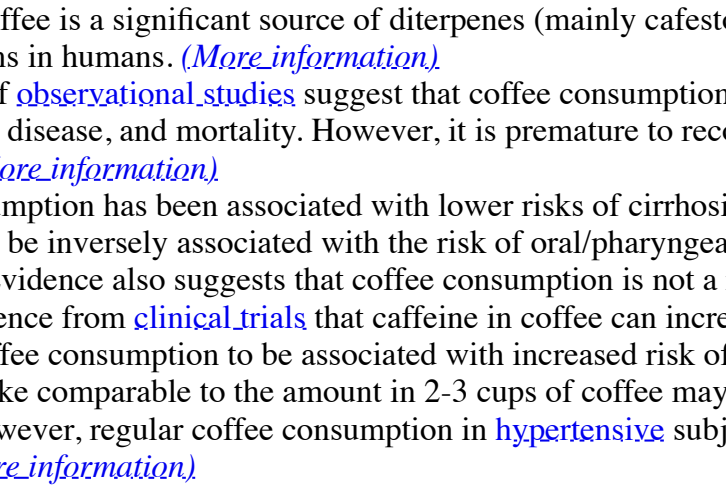
Coffee, an infusion of ground, roasted coffee beans, is among the most widely consumed beverages in the world. The main types of coffee consumed are (1) boiled unfiltered coffee, (2) filtered coffee, and (3) decaffeinated coffee (1). Although caffeine has received the most attention from scientists, coffee is a complex mixture of many chemicals, including carbohydrates, lipids (fats), amino acids, vitamins, minerals, alkaloids, and phenolic compounds (2). The composition of coffee varies with the source of coffee beans (*Coffea arabica* or *Coffea canephora* var. *robusta*) (3), as well as with the method of preparation (i.e., filtration methods, boiling, steeping, or brewing under pressure) (1, 4).

Some Bioactive Compounds in Coffee

Chlorogenic acids

Chlorogenic acids are a family of esters formed between quinic acid and phenolic compounds known as cinnamic acids (mostly caffeic acid and ferulic acid) (1). The most abundant chlorogenic acid in coffee is 5-*O*-caffeoylquinic acid, an ester formed between quinic acid and caffeic acid (**Figure 1**). Coffee represents one of the richest dietary sources of chlorogenic acids. The chlorogenic acid content of a 200 mL (7-oz) cup of coffee has been reported to range from 70 to 350 mg, which would provide about 35 to 175 mg of caffeic acid. Although chlorogenic and caffeic acids have demonstrated antioxidant activities *in vitro* (5), it is unclear how much antioxidant activity they contribute *in vivo* because they are extensively metabolized, and the metabolites often have lower antioxidant activity than the parent compounds (6, 7). Additionally, the antioxidant capacity of coffee is attenuated by the decaffeination process, which decreases total polyphenol content (8). Other phenolic compounds in coffee, though less abundant than chlorogenic acids, include tannins, lignans, and anthocyanine (1).

Figure 1. Chemical Structure of a Chlorogenic Acid



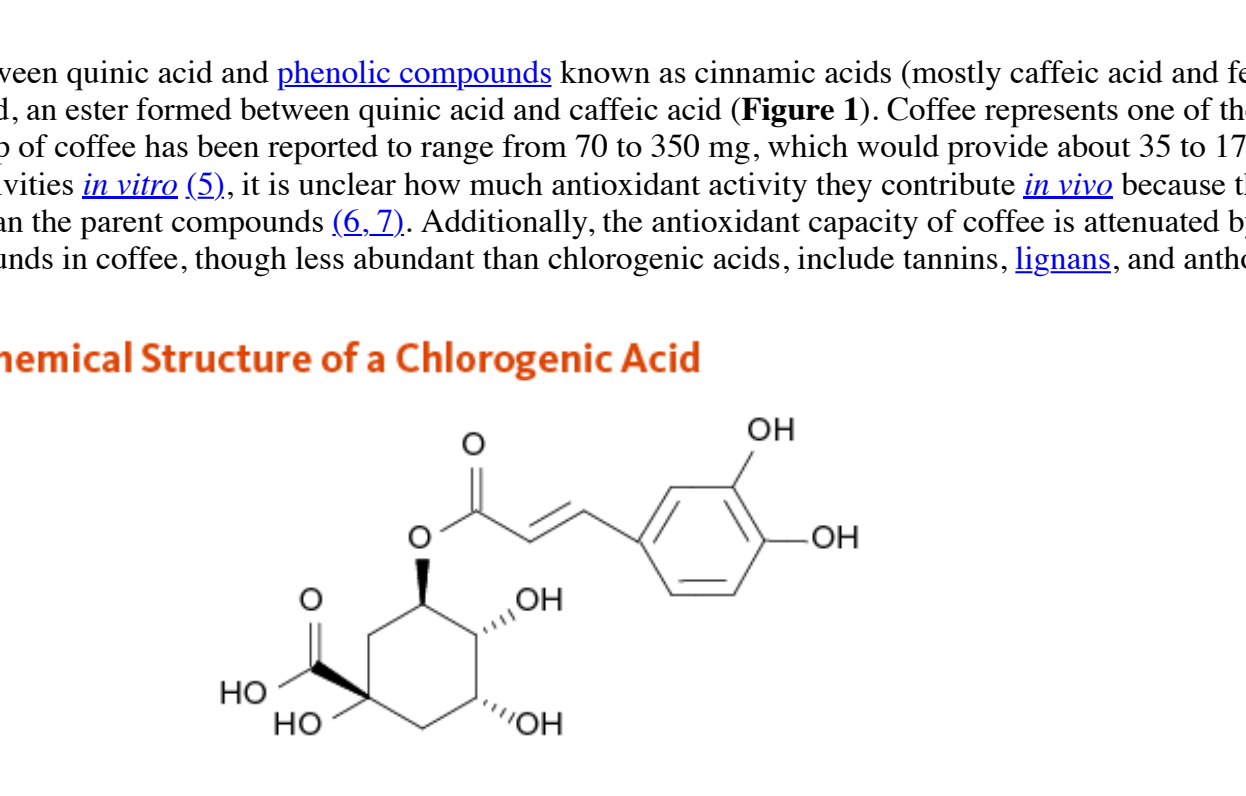
5-*O*-caffeoylquinic acid

[Figure 1 - Click to Enlarge]

Caffeine

Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid that occurs naturally in coffee beans (**Figure 2**). At intake levels associated with coffee consumption, caffeine appears to exert most of its biological effects through antagonism of the A$_1$ and A$_{2A}$ subtypes of the adenosine receptor (1). Adenosine is an endogenous compound that modulates the response of neurons to neurotransmitters. Adenosine has mostly inhibitory effects in the central nervous system, so the effects of adenosine antagonism by caffeine are generally stimulatory. Caffeine is rapidly and almost completely absorbed in the stomach and small intestine and then distributed to all tissues, including the brain. Caffeine concentrations in coffee beverages can be quite variable. A standard cup of coffee is often assumed to provide 100 mg of caffeine, but an analysis of 14 different specialty coffees purchased at coffee shops in the US found that the amount of caffeine in 8 oz (~240 mL) of brewed coffee ranged from 72 to 130 mg (9). Caffeine in espresso coffees ranged from 58 to 76 mg in a single shot (~35 to 50 mL). In countries other than the US, coffee is often stronger, but the volume per cup is smaller, making 100 mg of caffeine/cup a reasonable estimate.

Figure 2. Chemical Structures of Caffeine and Adenosine

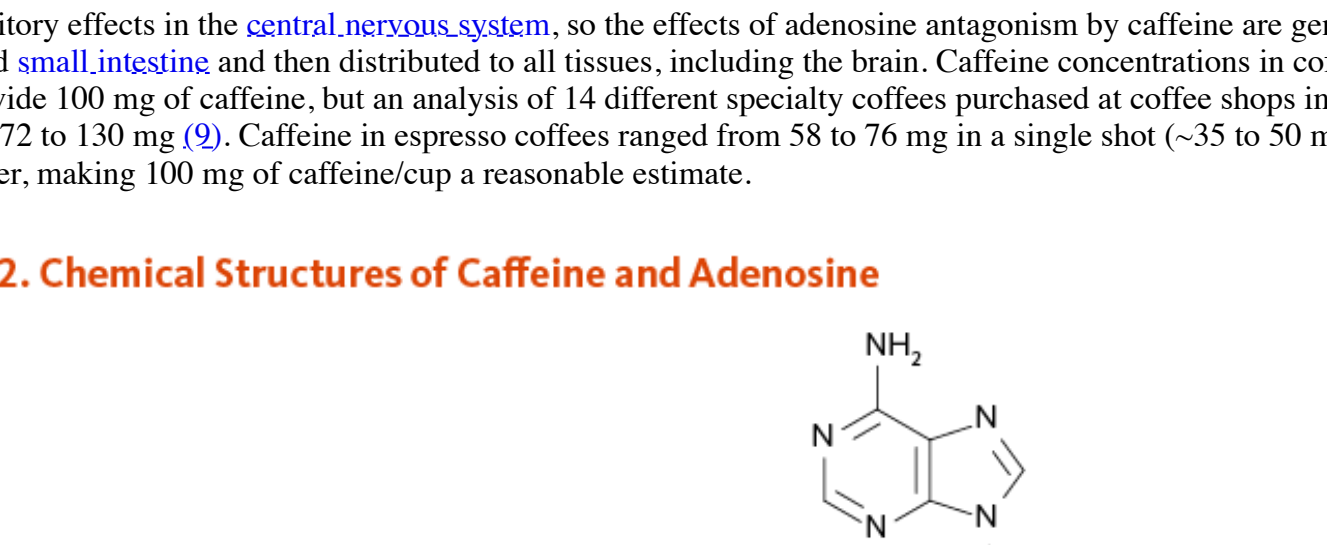


[Figure 2 - Click to Enlarge]

Diterpenes

Cafestol and kahweol are fat-soluble compounds known as diterpenes (**Figure 3**), which have been found to raise serum total and LDL-cholesterol concentrations in humans (10). Some cafestol and kahweol are extracted from ground coffee during brewing, but are largely removed from coffee by paper filters. Scandinavian boiled coffee, Turkish coffee, and French press (cafetiere) coffee contain relatively high levels of cafestol and kahweol (6 to 12 mg/cup), while filtered coffee, percolated coffee, and instant coffee contain low levels of cafestol and kahweol (0.2 to 0.6 mg/cup) (11). Although diterpene concentrations are relatively high in espresso coffee, the small serving size makes it an intermediate source of cafestol and kahweol (4 mg/cup). Since coffee beans are high in cafestol and kahweol, ingestion of coffee beans or grounds on a regular basis may also raise serum total and LDL-cholesterol.

Figure 3. Chemical Structures of Two Diterpenes



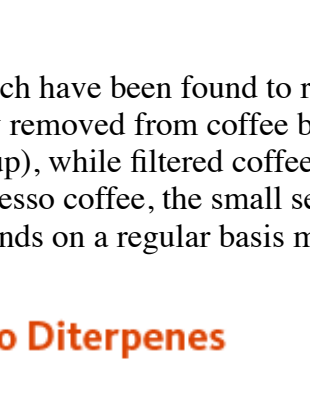
Free diterpene: R=H
Diterpene ester: R=fatty acid

[Figure 3 - Click to Enlarge]

Trigonelline

Trigonelline (*N*-methylnicotinic acid) is a plant alkaloid derived from niacin (vitamin B$_3$) (**Figure 4**). Trigonelline is largely broken down to nicotinic acid during the roasting process, although some intact molecules remain in roasted beans. Trigonelline has been found to exert antioxidant, hypoglycemic, and hypolipidemic activities (reviewed in 1).

Figure 4. Chemical Structure of Trigonelline



Trigonelline

[Figure 4 - Click to Enlarge]

Disease Prevention

Type 2 diabetes mellitus

Observational studies

The three largest prospective cohort studies in the US to examine the relationship between caffeinated coffee consumption and type 2 diabetes mellitus were the Health Professionals Follow-up Study ([HPFS]; 41,934 men), the Nurses' Health Study ([NHS I]; 84,276 women), and the NHS II (88,259 women). Men who drank at least six cups of coffee daily had a 54% lower risk of developing type 2 diabetes than men who did not drink coffee. In the NHS I cohort, women who drank at least six cups of coffee daily had a 29% lower risk of type 2 diabetes than women who did not drink coffee (12). In the NHS II cohort, women who consumed ≥4 cups of coffee daily had a 39% lower risk of developing type 2 diabetes; similar results were found in women who drank 2 to 3 cups/day of coffee (13). In a pooled analysis of all three cohorts, an increase in caffeinated coffee intake by >1 cup/day over a four-year period was associated with a 13% decreased risk of type 2 diabetes in the subsequent four years; those who decreased their intake of caffeinated coffee by >1 cup/day had a 20% increased risk of type 2 diabetes over the four-year period (14).

Several other cohort studies have found higher coffee intakes to be associated with significant reductions in the risk of type 2 diabetes. A systematic review and meta-analysis of 18 prospective cohort studies (published between 1966 and 2009), including more than 450,000 men and women, found that the risk of developing type 2 diabetes was 24% lower in those consuming 3 to 4 cups/day of coffee compared to those consuming ≤2 cups/day or none (15). Two additional meta-analyses that included data from more recent prospective cohort studies were published concomitantly and found similar results (16, 17). The data analysis of 28 prospective studies in over 1 million participants with 45,335 incident cases of diabetes reported a 30% decreased risk of type 2 diabetes with coffee intake of 5 cups/day versus 0 cups/day (16). In addition, a 9% reduction in the incidence of type 2 diabetes was estimated for every one cup per day increase in total coffee intake. Likewise, a dose-response analysis of 11 studies found a 6% reduction in type 2 diabetes incidence for every one cup per day increase in decaffeinated coffee intake. Every 140 mg/day (~1 cup/day of coffee) increment in caffeine intake was also associated with an 8% reduction in the risk of type 2 diabetes (16). Although decaffeinated coffee consumption is associated with a more modest decrease in the risk of type 2 diabetes, it is likely that compounds other than caffeine contribute to the reduction in diabetes risk.

Intervention studies

The mechanisms that might contribute to the association between coffee consumption and lower risk of type 2 diabetes in prospective cohort studies are unclear. Bioactive compounds other than caffeine appear to show temporary hypoglycemic effects. For example, the acute ingestion of chlorogenic acid (1 g) and trigonelline (0.5 g) transiently lowered blood glucose concentration shortly after the administration of 75 g of glucose in an oral glucose tolerance test (18). Conversely, short-term clinical trials have found that acute administration of caffeine (3 to 6 mg/kg) impaired glucose tolerance and decreased insulin sensitivity in healthy participants (19). In addition, incremental doses of decaffeinated coffee (1, 2, and 4 servings) failed to lower postprandial blood glucose in the presence of 100 mg of caffeine (20). However, despite the deleterious effect of caffeine on glucose homeostasis, caffeinated coffee consumption may favorably affect other metabolic pathways. In a single-blinded clinical trial, subjects at risk for type 2 diabetes abstained from drinking caffeinated coffee for one month, then consumed 4 cups/day of coffee for another month, and finally consumed 8 cups/day for a third month. Compared to one month of coffee abstinence, the consumption of 8 cups/day of coffee for one month appeared to increase antioxidant capacity and reduce subclinical inflammation, as indicated by changes in plasma markers of oxidative stress and inflammation (21).

Until the relationship between long-term coffee consumption and type 2 diabetes risk is better understood, it is premature to recommend coffee consumption as a means of preventing type 2 diabetes (12, 22).

Parkinson's disease

Studies in animal models of Parkinson's disease suggest that caffeine may protect dopaminergic neurons by acting as an adenosine A$_{2A}$-receptor antagonist in the brain (23). Several large prospective cohort studies have examined coffee and/or caffeine intakes in association with Parkinson's disease risk. A meta-analysis of nine prospective cohort studies found higher caffeine intake to be associated with significant reductions in Parkinson's disease risk in both men (-39%) and women (-29%) (24). In another meta-analysis of six case-control studies and seven prospective studies, including 901,764 participants and 3,954 cases, an inverse association between coffee intake and Parkinson's disease risk — only significant in men — was found to be nonlinear, with no further risk reduction beyond 3 to 4 cups/day of coffee. This meta-analysis also reported significant reductions in Parkinson's disease risk in men (-43%) and women (-36%) with the highest (700 mg/day) versus lowest (100 mg/day) intake of caffeine (25).

However, while prospective studies have consistently found a lower risk of developing Parkinson's disease with higher coffee and caffeine intakes in men, such an association has not always been observed in women (26-28). It is hypothesized that estrogen replacement therapy may modify the interaction between caffeine and risk of Parkinson's disease in postmenopausal women. Indeed, because estrogen and caffeine are metabolized by hepatic cytochrome P450 (CYP) 1A2 in the body, estrogen might compete for CYP1A2 activity and hinder the metabolism of caffeine in estrogen users (29). An analysis of data from more than 77,000 female nurses, followed for 18 years in NHS I, revealed that coffee consumption was inversely associated with Parkinson's disease risk in women who had never used postmenopausal estrogen (30). However, drinking ≥6 cups of coffee was associated with an increased risk or Parkinson's disease in women who had used postmenopausal estrogen (30). In a prospective cohort study that included more than 238,000 women, a significant inverse association between coffee consumption and Parkinson's disease mortality was also observed in women who had never used postmenopausal estrogen, but not in those who had used postmenopausal estrogen (31). Yet, in a recent analysis of the National Institutes of Health (NIH)-AARP Diet and Health Study, which included 303,880 participants and 1,100 cases, the highest versus lowest intake of caffeine was associated with a reduced risk of Parkinson's disease in postmenopausal women who ever used hormones but not among never users (24).

At present, it remains unclear whether caffeine consumption can prevent Parkinson's disease, particularly in women taking estrogen. Of note, whether caffeine could help reduce some common symptoms associated with Parkinson's disease (e.g., sleepiness, freezing of gait) is under investigation (32, 33).

Cognitive decline and dementia

Results from observational studies regarding a possible link between coffee consumption and cognitive disorders are inconclusive. A recent meta-analysis of nine prospective cohort studies in 34,282 older adults reported an 18% reduced risk of cognitive disorders with 1 to 2 cups/day of coffee compared to <1 cup/day (34). Yet, there was no difference in risk of cognitive disorders between daily coffee intakes >3 cups and <1 cup (34). Two other meta-analyses of prospective studies failed to find an association between high versus low intakes of coffee and risk of cognitive disorders (35, 36). No dose-response relationship was reported between coffee intake and risk of cognitive disorders (36).

Whether moderate coffee intake may reduce the risk of cognitive decline and dementia later in life is still not known.

Cirrhosis and liver cancer

Chronic inflammation-inducing liver injury may result in cirrhosis. In cirrhosis, the formation of fibrotic scar tissue leads to the progressive deterioration of liver function and other complications, including liver cancer (primarily hepatocellular carcinoma [HCC]) (37). The most common causes of cirrhosis in developed countries are alcohol abuse and chronic infections with hepatitis B and C viruses. Often associated with metabolic disorders, nonalcoholic fatty liver disease (NAFLD) is a liver condition that can progress to nonalcoholic steatohepatitis (NASH) in about one-third of NAFLD patients, thereby increasing the risk of cirrhosis and HCC (38).

A cross-sectional study in 177 subjects with chronic liver disease (especially chronic hepatitis B or C and NASH) found an association between daily caffeine intake >308 mg — equivalent to >2 cups/day of coffee — and a lower risk of having advanced liver fibrosis (39). Of note, no association was reported with non-coffee sources of caffeine like caffeinated soda or green and black tea (39). Recent cross-sectional studies also suggested a protective association of coffee intake against fibrosis development in patients with hepatitis C (40, 41). Additional studies have suggested that consumption of coffee, but not of caffeine, was inversely associated with the risk of advanced liver fibrosis in patients with NAFLD or NASH (42-44).

A recent meta-analysis of four case-control and three prospective cohort studies reported an inverse association between coffee consumption and risk of cirrhosis (45). In addition, a few large prospective cohort studies found that coffee drinking was associated with reduced mortality from alcoholic cirrhosis (46-49). A 17-year study of more than 51,000 men and women in Norway found that those who consumed ≥2 cups/day of coffee had a risk of cirrhosis-related death that was 40% lower than those who never consumed coffee (49). A 22-year prospective cohort study in 125,580 US adults found that coffee drinking was protective against alcoholic cirrhosis but not nonalcoholic cirrhosis (48). Specifically, the risk of developing alcoholic cirrhosis was 40% lower in those who drank 1 to 3 cups/day of coffee and 80% lower in those who drank ≥4 cups/day (48). Recent data from 63,275 Chinese participants of the Singapore Chinese Health Study showed that consumption of ≥2 cups/day of coffee was associated with a 66% lower risk of death from non-viral hepatitis-related cirrhosis — no such association was found with mortality from cirrhosis due to viral hepatitis (46).

Several case-control and prospective cohort studies have found significant inverse associations between coffee consumption and the risk of HCC (reviewed in 50). In a recent 18-year prospective cohort study of 162,022 US adults — comprising Japanese Americans, Caucasians, Mexican Americans, African Americans, and Native Hawaiians — consumption of coffee, but not decaffeinated coffee, was inversely associated with risk of developing HCC (51). Specifically, drinking 2 to 3 cups/day of coffee was associated with a 38% reduced risk of HCC compared to no coffee drinking (51). In addition, the risk of chronic liver disease-related mortality was 71% lower in individuals consuming ≥4 cups/day of regular coffee and 46% lower in those consuming ≥2 cups/day of decaffeinated coffee compared to non-consumers (51). A pooled analysis of this study with 10 other prospective cohort studies found an overall 46% lower risk of liver cancer with coffee consumption (see also Cancer) (52).

Cancer

Numerous observational studies have examined the relationship between coffee consumption and cancer risk (53, 54). Results from recently published meta-analyses of observational studies are reported in **Table 1**. In addition, a recent meta-analysis of prospective cohort studies by Wang et al. (54) investigated the relationships between the highest versus lowest categories of coffee intake and the risk of most cancer types. Coffee consumption was found to be associated with reduced risks of oral/pharyngeal cancer (6 studies; -31%), colon cancer (10 studies; -13%), liver cancer (9 studies; -54%), prostate cancer (14 studies; -11%), endometrial cancer (12 studies; -27%), and melanoma (6 studies; -11%) (54). Overall, these results are in agreement with those from other pooled analyses of prospective studies presented in **Table 1**. However, unlike the results reported by Wang et al. (54), coffee consumption has been inversely associated with the risk of colon cancer in case-control studies, but not in prospective cohort studies (see **Table 1**). Also, in the case of prostate cancer, several meta-analyses suggested a reduced risk with increased coffee intake in prospective but not case-control studies (54-56). However, whether this association exists only in certain study populations or at specific cancer stages remains unclear (57, 58). There seems to be little evidence of associations between coffee consumption and breast cancer, esophageal cancer, glioma, laryngeal cancer, pancreatic cancer, rectal cancer, stomach cancer, and thyroid cancer (**Table 1**) (54).

Table 1. Coffee and Cancer Risk: Meta-Analyses of Observational Studies

Type of Cancer	Type of Observational Studies	Relative Risk [RR] or Odds Ratio [OR]# (95% Confidence Interval)	Relative Risk [RR] or Odds Ratio [OR] in Subgroup Analyses (e.g., by study types)	References
Breast cancer	10 case-control and 16 prospective cohort studies	RR: 0.96 (0.93-1.00)	RR: 0.93 (0.86-1.00) for case-control studies RR: 0.98 (0.93-1.02) for cohort studies RR: 0.81 (0.67-0.97) for ER-negative cancer RR: 1.01 (0.93-1.09) for ER-positive cancer	Li et al. (2013; 59)
	20 case-control and 17 prospective cohort studies	RR: 0.97 (0.93-1.00)	RR: 0.94 (0.89-1.00) for case-control studies RR: 0.98 (0.95-1.02) for cohort studies RR: 0.99 (0.94-1.04) for caffeine RR: 0.98 (0.92-1.05) for decaffeinated coffee RR: 0.69 (0.53-0.89) among BRCA1 mutation carriers	Jiang et al. (2013; 60)
Colorectal cancer	25 case-control studies	OR: 0.85 (0.75-0.97)	OR: 0.68 (0.57-0.81) for colon cancer OR: 0.95 (0.79-1.15) for rectal cancer	Li et al. (2013; 61)
	16 prospective cohort studies	RR: 0.94 (0.88-1.01)	RR: 0.93 (0.86-1.01) for colon cancer RR: 0.98 (0.88-1.09) for rectal cancer	Li et al. (2013; 61)
	7 case-control and 5 prospective cohort studies	-	RR: 0.78 (0.65-0.95) for case-control studies RR: 0.82 (0.65-1.02) for cohort studies	Akter et al. (2016; 62)
	19 prospective cohort studies	RR: 0.98 (0.90-1.06)	RR: 0.92 (0.83-1.02) for colon cancer RR: 1.06 (0.95-1.19) for rectal cancer	Gan et al. (2017; 63)
Endometrial cancer	10 case-control and 6 prospective cohort studies	RR: 0.71 (0.62-0.81)	RR: 0.69 (0.55-0.87) for case-control studies RR: 0.70 (0.61-0.80) for cohort studies	Je et al. (2012; 64)
	13 prospective cohort studies	RR: 0.80 (0.74-0.86)	RR: 0.66 (0.52-0.84) for caffeinated coffee RR: 0.77 (0.63-0.94) for decaffeinated coffee	Zhou et al. (2015; 65)
Esophageal cancer	10 case-control and 4 prospective cohort studies	RR: 0.88 (0.76-1.01)		Zheng et al. (2013; 66)
Glioma	2 case-control and 4 prospective cohort studies	RR: 1.01 (0.83-1.22)		Malerba et al. (2013; 67)
Laryngeal cancer	5 case-control studies and 1 prospective cohort study	RR: 1.47 (1.03-2.11)		Chen et al. (2014; 68)
	7 case-control studies and 1 prospective cohort study	RR: 1.22 (0.92-1.62)		Ouyang et al. (2014; 69)
Liver cancer	10 prospective cohort studies	RR: 0.55 (0.44-0.67)	RR: 0.57 (0.42-0.79) for women RR: 0.58 (0.40-0.83) for men	Yu et al. (2016; 52)
Lung cancer	12 case-control and 5 prospective cohort studies	OR: 1.31 (1.11-1.55)	OR: 1.36 (1.10-1.69) for hospital-based case-control studies OR: 0.99 (0.77-1.28) for community-based case-control studies OR: 1.59 (1.26-2.00) for cohort studies OR: 1.41 (1.21-1.63) for men OR:1.16 (0.86-1.56) for women OR: 1.24 (1.00-1.54) for smokers OR: 0.85 (0.64-1.11) for non-smokers	Xie et al. (2016; 70)
Melanoma	4 case-control and 8 prospective cohort studies	RR: 0.80 (0.69-0.93)	RR: 0.85 (0.71-1.01) for caffeinated coffee RR: 0.92 (0.81-1.05) for decaffeinated coffee	Wang et al. (2016; 71)
Oral cancer	9 case-control and 3 prospective cohort studies	RR: 0.69 (0.54-0.89)	RR: 0.65 (0.46-0.92) for case-control studies RR: 0.81 (0.62-1.05) for cohort studies RR: 0.81 (0.58-1.13) for studies in the US RR: 0.57 (0.38-0.86) for studies in Europe	Zhang et al. (2015; 72)
Pancreatic cancer	22 case-control and 15 prospective cohort studies	RR: 1.08 (0.94-1.25)	RR: 1.10 (0.92-1.31) for case-control studies RR: 1.04 (0.80-1.36) for cohort studies	Turati et al. (2012; 73)
	20 prospective cohort studies	RR: 0.88 (0.64-1.12)		Ran et al. (2016; 74)
	21 prospective cohort studies	RR: 0.99 (0.81-1.21)		Nie et al. (2016; 75)
Prostate cancer	12 case-control and 12 prospective cohort studies	RR: 0.94 (0.85-1.05)	RR: 1.36 (1.06-1.75) for studies in the US RR: 1.08 (0.80-1.45) for studies in Europe RR: 0.92 (0.66-1.28) for studies in Asia RR: 0.61 (0.42-0.90) for fatal cancer RR: 0.70 (0.52-0.94) for high-grade tumors RR: 1.07 (0.89-1.29) for low-grade tumors	Zhong et al. (2014; 58)
	12 case-control and 9 prospective cohort studies	RR: 0.91 (0.86-0.97)	RR: 0.91 (0.95-1.26) for case-control studies RR: 0.89 (0.84-0.95) for cohort studies	Lu et al. (2014; 56)
	13 prospective cohort studies	RR: 0.90 (0.85-0.95)	RR: 0.93 (0.87-1.00) for studies in the US RR: 0.83 (0.75-0.92) for studies in Europe RR: 0.82 (0.51-1.31) for studies in Asia RR: 0.76 (0.55-1.06) for fatal cancer RR: 0.82 (0.61-1.10) for advanced tumors RR: 0.89 (0.83-0.96) for non-advanced tumors	Liu et al. (2015; 57)
Stomach cancer	9 prospective cohort studies	RR: 1.18 (0.90-1.55)		Zeng et al. (2015; 76)
	13 prospective cohort studies	RR: 1.13 (0.94-1.35)	RR: 1.36 (1.06-1.75) for studies in the US RR: 1.08 (0.80-1.45) for studies in Europe RR: 0.92 (0.66-1.28) for studies in Asia	Li et al. (2015; 77)
	13 case-control and 9 prospective cohort studies	RR: 0.96 (0.82-1.12)	RR: 0.85 (0.77-0.95) for case-control studies RR: 1.12 (0.94-1.33) for cohort studies	Xie et al. (2016; 78)
Thyroid cancer	5 case-control and 2 prospective cohort studies	OR: 0.88 (0.71-1.07)		Han et al. (2017; 79)

#Odds ratio or relative risk of cancer for the highest vs. lowest categories of coffee intake.

Finally, there is some evidence suggesting a potential increase in the risk of lung cancer with the highest versus lowest levels of coffee intakes. Yet, cigarette smoking has a major confounding effect on this association (see Health risks associated with coffee consumption) (54, 70).

Mortality

Three large US prospective cohort studies, namely NHS I (74,890 women), NHS II (93,054 women), and HPFS (40,557 men), examined whether coffee drinking was associated with all-cause, cardiovascular disease-related, or cancer-related mortality (80). Compared to no coffee consumption, the consumption of coffee, whether caffeinated or decaffeinated, up to 5 cups/day, was inversely associated with all-cause mortality. There was no difference in risk of death between non-consumers and consumers of >5 cups/day of coffee. Coffee consumption was also found to be inversely associated with mortality related to cardiovascular disease, neurological disease, and suicide (80). Other large cohort studies have reported habitual consumption of any coffee being inversely associated with all-cause and cardiovascular disease-related mortality, but generally not with cancer-related mortality (81-86). Moreover, the associations have not always been consistent among women and men, especially regarding cancer-related mortality (85, 86). A dose-response meta-analysis of 21 prospective studies found a nonlinear inverse association between coffee consumption and all-cause and cardiovascular disease-related mortality (87). Consumption of only 1 cup/day of coffee was significantly associated with lower risk of all-cause (-8%) and cardiovascular disease-related mortality (-11%). The largest risk reductions for all-cause (-16%) and cardiovascular disease-related mortality (-21%) were found to be associated with the consumption of 4 cups/day and 3 cups/day of coffee, respectively (87).

Safety

Adverse effects

Most adverse effects attributed to coffee consumption are related to caffeine. In healthy adults, daily caffeine consumption ≤400 mg — corresponding to 6.5 mg/kg body weight/day for a 70-kg person — is usually not associated with adverse effects (88). Caffeine intakes of less than 300 mg/day in women of childbearing age (equivalent to 4.3 mg/kg body weight/day for a 70-kg woman) and less than 2.5 mg/kg body weight/day in children are unlikely to cause adverse effects (88).

Adverse reactions to caffeine may include tachycardia (rapid heart rate), palpitations, insomnia, restlessness, nervousness, tremor, headache, abdominal pain, nausea, vomiting, diarrhea, and diuresis (increased urination) (89). Very high caffeine intakes, not usually from coffee, may induce hypokalemia (abnormally low serum potassium) (90). Sudden cessation of caffeine consumption after long-term use may result in caffeine withdrawal symptoms (91). Gradual withdrawal from caffeine appears less likely to result in withdrawal symptoms than abrupt withdrawal (92). Commonly reported caffeine withdrawal symptoms include headache, fatigue, drowsiness, irritability, difficulty concentrating, and depressed mood.

Potential health risks associated with regular coffee consumption

Cardiovascular disease

Serum lipids: An early meta-analysis of nine randomized controlled trials found that the consumption of unfiltered, boiled coffee dose-dependently increased serum total and LDL-cholesterol concentrations, while the consumption of filtered coffee resulted in very little change (93). A more recent meta-analysis of 12 randomized controlled trials reported that the consumption of coffee increased serum total cholesterol by 8.1 mg/dL, LDL-cholesterol by 5.1 mg/dL, and triglycerides by 12.6 mg/dL (94). The consumption of filtered coffee raised total cholesterol by only 3.6 mg/dL compared to an increase of 12.9 mg/dL with unfiltered coffee consumption. Unlike filtered coffee, consumption of unfiltered coffee significantly increased LDL-cholesterol and triglycerides by 11.9 mg/dL and 18.8 mg/dL, respectively (94). The cholesterol-raising factors in unfiltered coffee have been identified as cafestol and kahweol, two diterpenes that are largely removed from coffee by paper filters (see Diterpenes) (10).

Homocysteine: An elevated plasma total homocysteine concentration has been associated with increased risk of cardiovascular disease, including coronary heart disease, stroke, and peripheral vascular disease, but the relationship may not be causal (95). Higher coffee intakes have been associated with increased plasma homocysteine concentrations in cross-sectional studies conducted in Europe, Scandinavia, and the US (96-100). Controlled clinical trials have confirmed the homocysteine-raising effect of coffee at intakes of about 4 cups/day (101-103).

Hypertension: Hypertension is a well-recognized risk factor for cardiovascular disease. Two meta-analyses of randomized controlled trials showed that high intakes of coffee (3 to 5 cups/day) for <85 days significantly increased systolic/diastolic blood pressure by 1.2/0.5 mm Hg (104) or 2.4/1.2 mm Hg (105). Although the increases in blood pressure seem modest by individual standards, it has been estimated that an average systolic blood pressure reduction of 2 mm Hg in a population may result in 10% lower mortality from stroke and 7% lower mortality from coronary heart disease (106). However, a more recent pooled analysis excluding the trials that used decaffeinated coffee in control groups — and thus assessed the effect of caffeine rather than that of coffee — found no significant changes in systolic blood pressure and diastolic blood pressure with high coffee intakes (107). Additionally, two meta-analyses combined the data from observational studies that examined prospectively the association between habitual coffee consumption and risk of hypertension (107, 108). One meta-analysis of six prospective cohort studies included 172,567 non-hypertensive participants (one study enrolled pre-hypertensive subjects) of which 37,135 cases of incident hypertension were reported over follow-up periods spanning from 6.4 years to 33 years (108). Compared to coffee intakes of <1 cup/day, intakes of 1 to 3 cups/day were found to be associated with a 9% increased risk of hypertension. However, no such association could be observed for coffee intakes >3 cups/day (108). Another meta-analysis of four prospective cohort studies found no association between coffee consumption and risk of hypertension (107). Also, a recent analysis of data from 29,985 postmenopausal women followed for nearly four years in the Women's Health Initiative Observational Study found no increased risk of hypertension with intakes of caffeinated coffee, decaffeinated coffee, or caffeine (109).

While there is little evidence of an association between long-term coffee consumption and risk of hypertension, the available evidence from trials suggests that consumption of caffeine modestly raises systolic blood pressure. Whether this may result in increased risk of stroke and coronary heart disease in the population, particularly in those with hypertension, is still uncertain. Yet, to date, regular coffee consumption in hypertensive subjects has not been associated with an increased risk of cardiovascular disease (110).

Coronary heart disease: A meta-analysis of 20 prospective cohort studies, including 407,806 participants and 15,599 incident coronary heart disease (CHD) cases, found no significant association between coffee consumption and CHD risk (111). Yet, a more recent meta-analysis of 22 prospective cohort studies reported a modest reduction in CHD risk with moderate (3-5 cups/day) — but not high (≥6 cups/day) — coffee intakes compared to low intakes (<1 cup/day) (112).

In addition, cross-sectional studies have provided little evidence that the formation of atherosclerotic plaques, an early event in the development of CHD, is more prevalent in regular coffee drinkers than in non-drinkers (113-116). Coffee consumption has not been linked to the development of atherosclerosis in two prospective cohort studies. In the Coronary Artery Risk Development in Young Adults (CARDIA) study that followed approximately 4,000 young US adults for 15 to 20 years, there was no evidence of an association between regular coffee intake and progression of coronary artery calcification, a measure of subclinical atherosclerosis (117). Moreover, in the Multi-Ethnic Study of Atherosclerosis (MESA) that followed about 6,500 US adults over a median period of 11.1 years, occasional but not regular drinking of coffee was associated with a 28% increased risk of cardiovascular disease compared with no drinking (114). This study found no association between coffee intake and progression of coronary artery calcification (114).

Cardiac arrhythmias: Early clinical trials found coffee or caffeine intake equivalent to 5 to 6 cups/day did not increas the frequency or severity of cardiac arrhythmias in healthy people or in people with coronary heart disease (118, 119). A meta-analysis of six prospective cohort studies in 214,316 participants found no association between coffee consumption and risk of atrial fibrillation, the most common type of cardiac arrhythmias. In addition, a recent meta-analysis of 11 short-term intervention studies (single dose to two-week trials) found that caffeine consumption did not increase the occurrence of ventricular arrhythmias (120). Finally, two meta-analyses of observational studies found no evidence to suggest that caffeine consumption was associated with an increased risk of atrial fibrillation and even reported a modest reduction in risk with moderate intakes (121, 122).

Thus, consumption of coffee or caffeine at usual intakes does not appear to increase the risk of cardiac arrhythmias. The current evidence does not support clinical recommendations that discourage moderate consumption of coffee in patients at risk or with suspicions of cardiac arrhythmia (120, 123).

Stroke: A 2011 meta-analysis that included eight prospective cohort studies — all following participants who were free of cardiovascular disease and diabetes mellitus at baseline — found that consumption of 3 to 4 cups/day of coffee was associated with an 18% lower risk of stroke compared with no consumption and that higher intakes were not associated with an increased risk (124). Since this meta-analysis, a few large prospective studies have reported mixed results on the association between coffee consumption and stroke incidence or stroke-related mortality. Results from 42,659 participants in the German cohort of the European Prospective Investigation in Cancer and Nutrition (EPIC-Germany) reported no association between coffee consumption and stroke incidence over an 8.9 year-period (125). Compared to no intake, consumption of ≥3-6 cups/week of coffee was associated with a reduced risk of stroke in a prospective study of 82,369 Japanese participants (126). Also, the consumption of 4 to 5 cups/day of coffee was associated with a reduced risk of stroke-related mortality among men, but not women, followed in the large prospective NIH-AARP Diet and Health Study (81).

Lung cancer

Several observational studies have examined the relationship between coffee intake and lung cancer risk in humans. A recent meta-analysis of 12 case-control and 5 prospective cohort studies, including a total of 12,276 cases and 102,516 controls, found an overall 31% increased risk of lung cancer with the highest versus lowest levels of coffee intake (see **Table 1**). Subgroup analyses outlined a significant increase in lung cancer risk with coffee intake in hospital-based case-control (+36%) and prospective cohort studies (+59%), in studies conducted in American (+34%) and Asian (+49%) populations, in men (+41%), and in smokers (+24%); conversely, no significant association between coffee intake and lung cancer risk was found in community-based case-control studies, in studies conducted in European populations, in women, and in non-smokers (70). Another meta-analysis of 13 case-control and 8 prospective cohort studies, including 19,892 cases and 623,645 controls, found a 9% increased risk of lung cancer in coffee drinkers compared to non-drinkers (127). However, a pooled analysis restricted to the 16 (out of 21) studies that adjusted for smoking found no significant association between coffee intake and risk of lung cancer [RR: 1.03 (0.95-1.12)].

Cigarette smoking is a major confounding factor in the association between coffee consumption and lung cancer risk, and the evidence suggests that coffee intake is unlikely to be a risk factor for lung cancer. Of note, residual confounding by smoking remains a concern when a slight increase in lung cancer risk is still observed in studies even after adjustment for tobacco smoking (127).

Adverse pregnancy outcomes

It has been suggested that *in utero* exposure to caffeine through maternal coffee consumption might have adverse effects on the embryo/fetus during pregnancy and the offspring.

Miscarriage: The results of observational studies that have examined the relationship between maternal coffee or caffeine intake and the risk of miscarriage (spontaneous abortion) have been conflicting. While some prospective cohort studies have observed significant associations between high caffeine intakes, particularly from coffee, and the risk of spontaneous abortion (128-132), other studies have not (133-136). The most recent meta-analysis of 14 prospective cohort studies in 130,456 pregnant women and 3,429 cases of miscarriage found risk of miscarriage increased by 40% and 72% with maternal caffeine intakes of 350 to 699 mg/day and ≥700 mg/day during pregnancy, respectively (137). No significant associations were found for daily doses of caffeine less than 350 mg. A dose-response analysis found a 7% increase in the risk of miscarriage per 100 mg/day-increment in caffeine intake during pregnancy (137). Of note, one prospective cohort study that assessed caffeine intake by measuring serum concentrations of paraxanthine, a caffeine metabolite, found that the risk of spontaneous abortion was only elevated in women with paraxanthine concentrations that suggested caffeine intakes of ≥600 mg/day (138).

It has been proposed that an association between caffeine consumption and the risk of spontaneous abortion could be explained by the relationship between nausea and fetal viability (139). Nausea is more common in women with viable pregnancies than nonviable pregnancies, such that women with viable pregnancies may be more likely avoid or limit caffeine consumption due to nausea (140). However, at least one study found that the significant increase in risk of spontaneous abortion observed in women with caffeine intakes >300 mg/day was independent of nausea in pregnancy (141). Additionally, two other studies found that caffeine consumption was associated with an increased risk of spontaneous abortion in women who experienced nausea or aversion to coffee during pregnancy (131, 142). Nonetheless, this does not exclude the possibility of reverse causality, when the loss of fetal viability results in reduction of pregnancy symptoms, like nausea and aversion to coffee, and may be followed by an increase in coffee intake (137).

Of note, consumption of <400 mg/day of caffeine or <4 cups/day of caffeinated coffee by women prior to pregnancy has not been linked to the risk of miscarriage in an analysis of a large prospective study (NHS I) that followed 11,072 women and a total of 15,590 pregnancies (143).

Although the topic remains unsettled, the American College of Obstetricians and Gynecologists recommends that women limit their daily caffeine intake to <200 mg during pregnancy (144).

Intrauterine growth restriction and low birth weight: Observational studies examining the effects of maternal caffeine and coffee consumption on fetal growth have assessed intrauterine growth restriction (IUGR; also known as small-for-gestational age; defined as fetal weight <10th percentile for gestational age), and/or incidence of low birth weight (defined as weight at birth <2,500 g [5.5 pounds]).

A recent meta-analysis of eight prospective cohort and four case-control studies reported a 38% increased risk of low birth weight with the highest versus lowest intakes of caffeine during pregnancy (145). This risk appeared to increase linearly with incremental doses of caffeine (145, 146). A dose-response meta-analysis of six prospective cohort and five case-control studies found a 7% increased risk of low-birth-weight infants per 100 mg of caffeine consumed daily during pregnancy (146). Likewise, a 100 mg-increment in maternal caffeine intakes has been associated with a 10% increased risk of small-for-gestational age infants in the dose-response analysis of 10 prospective cohort and 5 case-control studies (146).

At present, only one study has examined the impact of limiting caffeine intake during pregnancy on birth weight. In a double-blind, intervention trial that randomized 1,197 regular coffee drinkers (≥3 cups/day of coffee) to drink decaffeinated (median caffeine intake of 117 mg/day) or caffeinated coffee (median caffeine intake of 317 mg/day) throughout the second half of their pregnancy, no differences in length of gestation or infant birth weight were found between the two groups (147).

Although the relationship between maternal caffeine consumption and fetal growth requires further clarification, it appears that even moderate caffeine intakes might adversely affect fetal growth in non-smoking women (145, 146, 148). Limiting caffeine intake to ≤100 mg/day (≤1 cup/day of coffee) during pregnancy may be recommended to avoid any adverse effect, assuming that the associations of caffeine intake with the risk of IUGR and low birth weight are causal (145, 146).

Birth defects: Potential relationships between coffee consumption during pregnancy and congenital birth defects have been investigated in the US population-based National Birth Defects Prevention Study (NBDPS), an ongoing multi-site case-control study. In an analysis that included mothers of 1,531 infants with cleft lips (with or without cleft palates), 813 infants with cleft palates only, and 5,711 control infants, no association was found between the highest versus lowest intakes of coffee and caffeine and the risk of orofacial clefts (149). Another analysis, including mothers of 3,346 cases and 6,642 control infants, suggested an increased risk of anotia/microtia and craniosynostosis with the consumption of coffee or caffeine. However, no dose-response could be detected (150). Further, an analysis of the NBDPS in mothers of 844 infants with limb deficiencies and 8,069 control infants found no increased risk associated with coffee and/or caffeine intake during pregnancy (151). There was no association between maternal coffee or caffeine intake during pregnancy and risk of congenital talipes equinovarus (known as "clubfoot") in another US population-based case-control study of mothers of 646 infants with isolated clubfoot and 2,037 control infants (152). Finally, a recent meta-analysis that combined data from one prospective cohort study and six case-control studies found no association between maternal coffee consumption during pregnancy and risk of neural tube defects (153).

At present, there is no convincing evidence that maternal consumption of 3 cups/day of coffee or 300 mg/day of caffeine during pregnancy increases the risk of congenital malformations in humans.

Childhood acute leukemia: The etiology of acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML), which primarily affect children, is unclear. It has been suggested that exposure to caffeine during pregnancy might have long-lasting adverse effects on the health of the offspring. A meta-analysis of seven case-control studies that examined maternal coffee consumption during pregnancy in relation to the incidence of childhood acute leukemia found coffee consumption was associated with increased risks of overall acute leukemia (+72%), ALL (+65%), and AML (+58%) (154). Another meta-analysis of eight case-control studies found an increased risk of ALL (+43%), but not AML, with the highest versus lowest intakes of coffee during pregnancy (155). High versus low consumption of other sources of caffeine during pregnancy (tea, cola beverages) and childhood (cola beverages) were not found to be associated with childhood acute leukemia (155).

The evidence of a positive association between maternal coffee intake and childhood acute leukemia is currently limited to case-control studies. Case-control studies usually include more cancer cases than prospective cohort studies, but they are subject to recall bias with respect to coffee consumption and selection bias with respect to the control group (156). Further studies with a prospective design are needed to confirm the possible link between coffee intake during pregnancy and childhood acute leukemia.

Lactation

The American Academy of Pediatrics categorizes caffeine as a maternal medication that is usually compatible with breast-feeding (157). Although high maternal caffeine intakes have been reported to cause irritability and poor sleeping patterns in infants, no adverse effects have been reported with moderate maternal intake of caffeinated beverages equivalent to 2 to 3 cups of coffee daily.

Nutrient interactions

Calcium, osteoporosis, and risk of fracture

Osteoporosis is a multifactorial bone disorder that compromises bone mass and strength and increases the risk of fracture. The results of early controlled studies in humans indicated that coffee and caffeine consumption decreased the efficiency of calcium absorption resulting in a loss of about 4 to 6 mg of calcium per cup of coffee (158, 159). However, there is little evidence to suggest detrimental effects of coffee on bone health in populations with adequate calcium intakes (160). To date, results from observational studies that examined associations between coffee intakes and measures of bone mineral density (BMD) loss — generally used to diagnose osteoporosis — have been mixed (161-164). Further, two meta-analyses of observational studies reported no significant associations between coffee intake and risk of hip fracture (165, 166). A third meta-analysis of six case-control and nine prospective cohort studies found no overall association between coffee intake and total fracture (167). Yet, a gender subgroup analysis of eight studies showed a 14% increased risk of fracture in women — but not in men — with the highest versus lowest intakes of coffee. Another subgroup analysis of six studies found a 35% increased risk of osteoporotic fracture in participants with the highest versus lowest intakes of coffee (167).

Current evidence is scarce to suggest that coffee consumption could increase the risk of bone loss and fracture. Limiting coffee consumption to ≤3 cups/day while ensuring adequate calcium and vitamin D intakes should prevent any potential adverse effects on calcium absorption and bone health.

Nonheme iron

Phenolic compounds in coffee can bind nonheme iron and inhibit its intestinal absorption (168). Drinking 150 to 250 mL of coffee with a test meal has been found to inhibit iron absorption by 24%-73% (169, 170). To maximize iron absorption from a meal or supplements, people with poor iron status should not consume coffee at the same time.

Drug interactions

Habitual caffeine consumption increases hepatic cytochrome P450 (CYP) 1A2 activity, which has implications for the metabolism for a number of medications (171). Conversely, drugs that inhibit the activity of CYP1A2 interfere with the metabolism and elimination of caffeine, thereby increasing the risk of adverse effects (172).

Drugs that alter caffeine metabolism

The following medications may impair the hepatic metabolism of caffeine, delaying its excretion and potentially increasing the risk of caffeine-related side effects: cimetidine (Tagamet), disulfiram (Antabuse), estrogens, fluconazole (Diflucan), fluvoxamine (Luvox), mexiletine (Mexitil), quinolone class antibiotics (Cipro, Avelox), riluzole (Rilutek), terbinafine (Lamisil), and Verapamil (Calan) (173). Concomitant use of ephedrine and caffeine can lead to life-threatening adverse effects, including heart attack, stroke, seizures, and death (173). Use of the drug phenytoin (Dilantin) or cigarette smoking increases the hepatic metabolism of caffeine, resulting in increased elimination and decreased plasma caffeine concentrations (89).

Caffeine effects on other drugs

Caffeine and other methylxanthines may enhance the effects and side effects of β-adrenergic stimulating agents, such as epinephrine and albuterol (89, 171). Caffeine doses of 400 to 1,000 mg may inhibit the hepatic metabolism of the antipsychotic medication, clozapine (Clozaril), potentially elevating serum clozapine concentration and increasing the risk of toxicity. Those taking levothyroxine are advised to avoid drinking coffee at the same time they take their medication because coffee may reduce the absorption of levothyroxine in some patients. Caffeine consumption can decrease the elimination of theophylline, potentially increasing serum theophylline levels. Caffeine has been also found to decrease the systemic elimination of acetaminophen (i.e., paracetamol) and to increase the bioavailability of aspirin, which may partially explain its efficacy in enhancing their analgesic effects. This is important because many pain-relievers on the market today combine caffeine with aspirin and/or acetaminophen. Further, caffeine may decrease the bioavailability of lithium and alendronate (Fosamax) by enhancing their elimination (173).

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Tea

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日本語

Summary

- Tea is an infusion of the leaves of the *Camellia sinensis* plant, which is not to be confused with herbal teas. *(More information)*
- All the tea types, including white, green, oolong, black, and Pu-erh tea, are produced from the leaves of the *Camellia sinensis* plant. Different processing methods yield the various types of tea. *(More information)*
- Biologically active chemicals in tea include flavonoids, caffeine, fluoride, and theanine. Green teas are especially rich in a group of flavonoids called flavan-3-ol monomers or catechins. Black teas contain more complex chemicals — theaflavins and thearubigins — derived from catechins. *(More information)*
- Observational studies in humans suggest that daily consumption of tea may be associated with a reduced risk of cardiovascular disease (CVD). Intervention studies showed that tea exhibited cholesterol-lowering, anti-inflammatory, antioxidant, and anti-hypertensive properties, which might be beneficial in the prevention of CVD. *(More information)*
- Tea consumption has been associated with reduced risk of developing type 2 diabetes mellitus in large prospective cohort studies. Yet, the mechanisms behind this association are complex, possibly involving a role for tea bioactive compounds in the regulation of energy balance, lipid and glucose metabolism, insulin sensitivity, body composition, and/or body temperature. *(More information)*
- Despite promising results from animal studies, current evidence does not support a role for tea consumption in the prevention of most cancers in humans. *(More information)*
- It is still unclear whether tea consumption is associated with increased bone mineral density and/or reduced risk of osteoporotic fractures. *(More information)*
- Limited research suggests an inverse association between tea consumption and risk of tooth cavities. The incorporation of green tea extract in mouthwashes and/or toothpastes may also help reduce dental plaque and gum inflammation in patients. *(More information)*
- The pooled analysis of three large US prospective cohort studies found an 11% lower risk of kidney stones with the highest versus lowest level of tea intake. More research is needed to assess whether the oxalate content in tea may affect subjects with a history of kidney stones. *(More information)*
- The mounting evidence for a role of tea consumption in the prevention of cognitive decline comes from observational studies. Clinical studies would be needed to establish whether tea or its bioactive constituents could limit cognitive decline and/or improve cognitive dysfunction in older individuals. *(More information)*
- The use of green tea extracts in clinical trials was found to cause gastrointestinal disorders and liver toxicity. Tea consumption may also potentially interfere with certain medications, including the anticoagulant, warfarin, and some cardiovascular drugs. *(More information)*

Introduction

Tea is an infusion of the leaves of the *Camellia sinensis* plant and, aside from water, is the most widely consumed beverage in the world (1). Different processing methods of tea leaves involve variable degrees of oxidation yielding different types of tea (green, oolong, or black tea). In 2014, Americans consumed 3.6 billion gallons of tea, of which 84% was black tea, 15% was green tea, and the remaining was white, oolong, and dark tea (2). Herbal teas are infusions of herbs or plants other than *Camellia sinensis* and will not be discussed in this article. Although tea contains a number of bioactive chemicals, including caffeine and fluoride, most research has focused on the potential health benefits of a class of compounds in tea known as flavonoids. In many cultures, tea is an important source of dietary flavonoids.

Definitions

Types of tea

All teas are derived from the leaves of the tea plant *Camellia sinensis*, but different processing methods produce different types of tea. Fresh tea leaves are rich in polyphenolic compounds known as flavonoids (see the article on Flavonoids). Flavonoids are divided in six subclasses: flavan-3-ols, anthocyanidins, flavanones, flavonols, flavones, and isoflavones (**Figure 1**). Tea leaves contain a polyphenol oxidase (PPO) enzyme in separate compartments from flavan-3-ol monomers or catechins (**Figure 2**) (3). When tea leaves are intentionally broken or rolled during processing, cell compartmentalization is disrupted and PPO comes into contact with catechins. This causes catechins to condense (join together) forming dimers and polymers known as theaflavins (**Figure 3**) and thearubigins, respectively (4). This oxidation process is often described as "fermentation" in the tea industry. Steaming, firing, or baking tea leaves inactivates PPO and stops the oxidation process (5).

The two prominent varieties of *Camellia sinensis* used in tea cultivation are *Camellia sinensis var. sinensis* and *Camellia sinensis var. assamica*. The former is native of China and usually used to make white and green tea. The latter originates from the Assam region of India, as well as regions of Southeast Asia, and is often used to make black teas, including pu-erh tea in the Yunnan province of China.

Although there are thousands of tea cultivars derived from the principal *Camellia sinensis* tea varieties, teas are usually divided into five types based on the extent of oxidation they undergo during processing. The withering method (the process of allowing the fresh leaves to dry) and the process of deactivating PPO may also differ among tea preparations (1).

Figure 1. Basic Structures of Flavonoid Subclasses

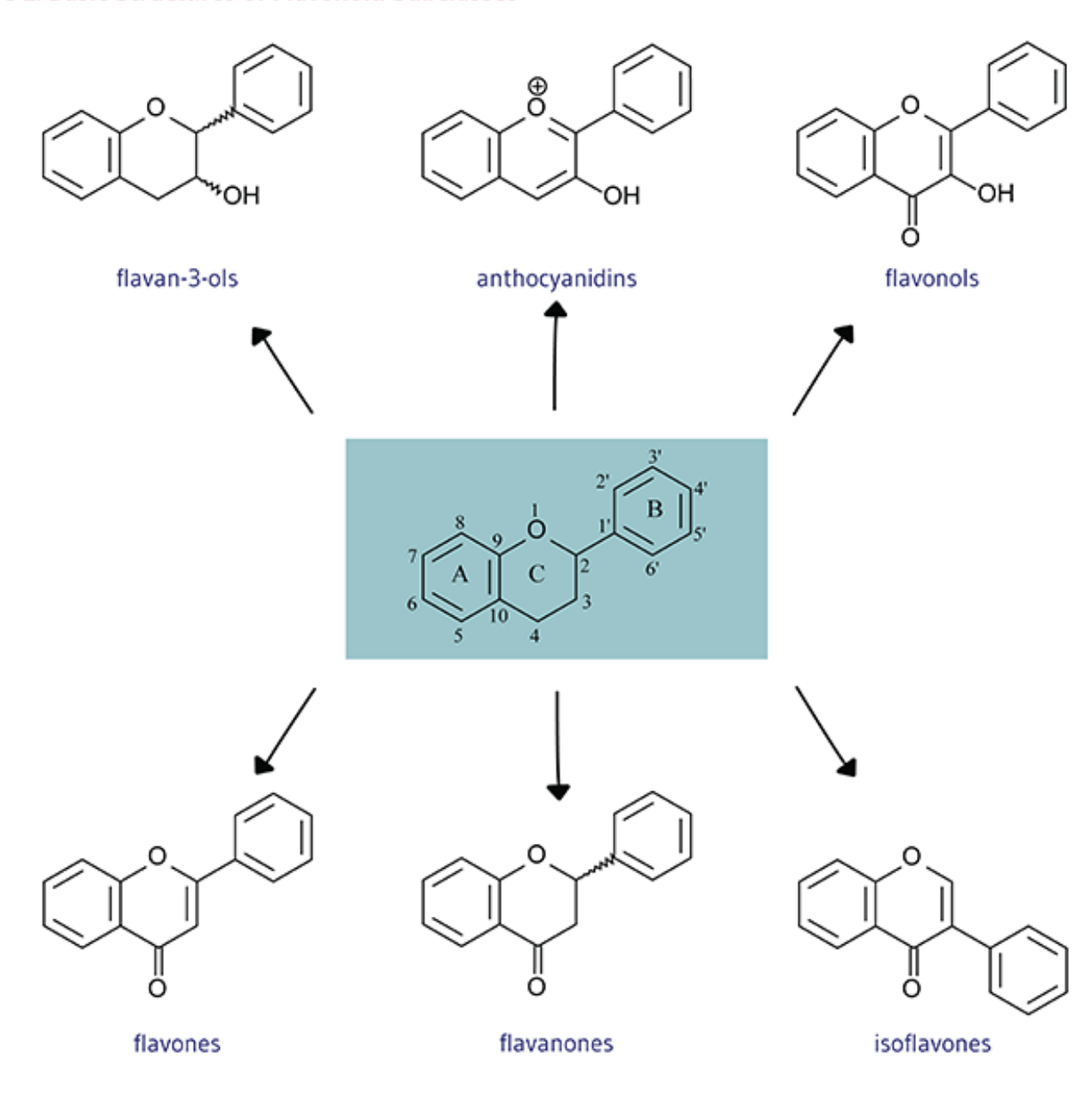


Figure 2. Chemical Structures of Principal Flavan-3-ols (Catechins) in Tea

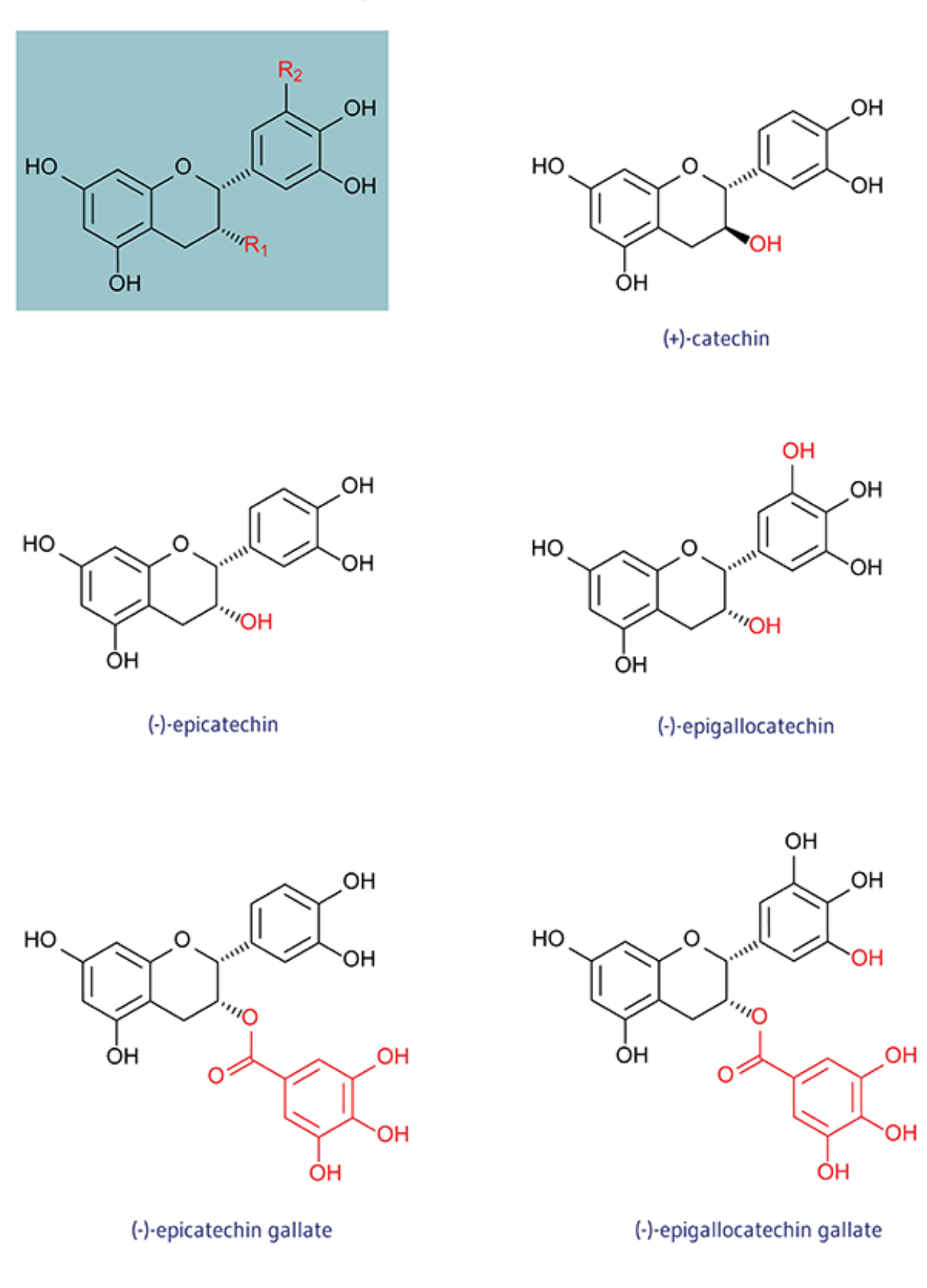
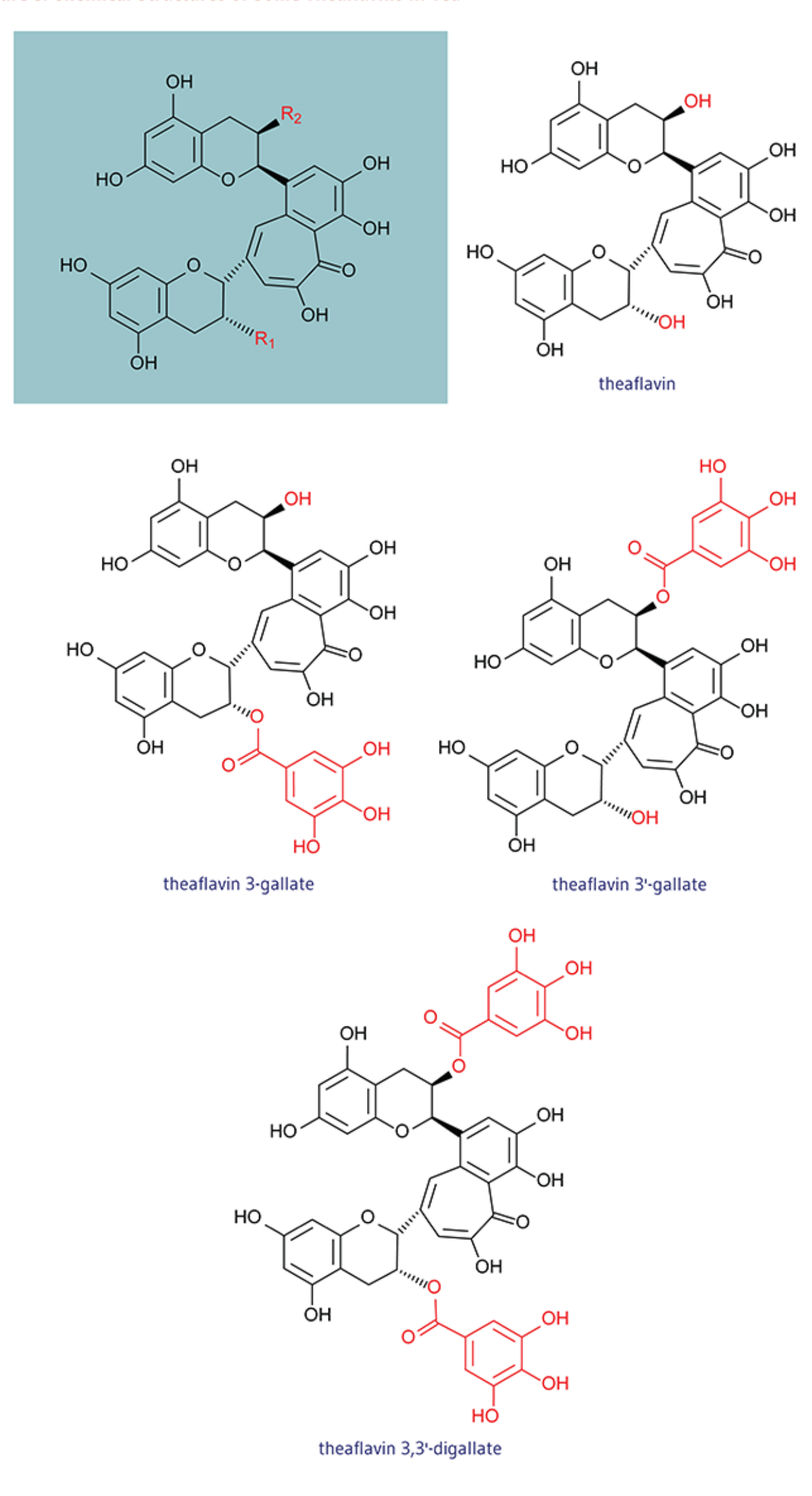


Figure 3. Chemical Structures of Some Theaflavins in Tea



White tea

White tea is made from unopened buds and immature leaves, which are steamed or fired to inactivate polyphenol oxidase, and then dried. Thus, due to minimal oxidation, white tea retains the high concentrations of catechins present in fresh tea leaves (see Flavonoids below).

Green tea

Green tea is made from more mature tea leaves than white tea, and tea leaves may be withered prior to steaming or firing, and then rolled and dried. Like white teas, green teas are high in catechins, but the total content and composition of catechins may vary depending on the cultivar and the commercial source (6). Of note, green teas and white teas may sometimes contain similar amounts of catechins but still exhibit different antioxidant capacities; this is due to the presence of other non-catechin antioxidants in teas (6).

Oolong (Wulong) tea

Tea leaves destined to become oolong teas are "bruised" to allow the release of some of the polyphenol oxidase present in the leaves. Oolong teas are allowed to oxidize to a greater extent than for white or green teas, but for less time than black teas, before they are heated and dried. Consequently, the catechin, theaflavin, and thearubigin levels in oolong teas are generally between those of unfermented green and white teas and completely oxidized black teas (1).

Black tea

Tea leaves destined to become black tea are fully rolled or broken to maximize the interaction between catechins and polyphenol oxidase. Because they are allowed to oxidize completely before drying, most black teas are relatively low in monomeric flavan-3-ols, like (-)-epigallocatechin gallate (EGCG), and rich in theaflavins (2%-6% of extracted solids) and thearubigins (>20% of extracted solids) (see **Table 1** below). Some theaflavins have shown greater antioxidant activities than EGCG (7).

Pu-erh tea (also pu'erh tea, pu'er tea, or Chinese black tea)

Most pu-erh tea is produced in the Yunnan province of China from the larger leaves of the *assamica* variety of *Camellia sinensis*. The making process may include both enzymatic oxidation and fungus-led fermentation. In the case of "raw (aged) pu-erh tea," the initial preparation resembles that used to make green tea. The leaves are heated, dried, and then dampened before being pan-fired and compressed; the preparation is then carefully stored in a controlled environment and left to age for decades. A faster aging process, combining oxidation and fermentation by the fungus *Aspergillus niger* for several months, can also be used to produce "ripened pu-erh tea."

Cup sizes

The definition of a cup of tea varies in different countries or regions. In Japan, a typical cup of green tea may contain only 100 mL (3.5 ounces). A traditional European teacup holds approximately 125 to 150 mL (5 ounces), while a mug of tea may contain about 240 mL (8 ounces).

Bioactive Compounds in Tea

Tea contains over 2,000 components, including polyphenols (flavonoids), pigments (carotenoids and chlorophyll), alkaloids (caffeine, theophylline, theobromine), lignans, carbohydrates, lipids, proteins, amino acids (including L-theanine), vitamins (vitamin C, vitamin E, riboflavin), and various minerals and trace elements (8). Only some of them are described below.

Flavonoids

Dietary flavonoids are divided in six subclasses: flavan-3-ols, anthocyanidins, flavanones, flavonols, flavones, and isoflavones (see the article on Flavonoids). Total flavonoid content in green tea and black tea is of about 138 mg and 118 mg per 100 mL, respectively (9). A major subclass of flavonoids in tea is that of flavan-3-ols. Flavan-3-ol monomers, also known as catechins, constitute 30%-42% of the solid weight of brewed green tea. The principal catechins found in tea are (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG) (see **Figure 2**). When catechins are enzymatically oxidized by polyphenol oxidase during the oxidation process that yields black tea, they form low molecular weight dimers known as theaflavins (see **Figure 3**) and complex polymers (of mostly unknown structures) called thearubigins. Non-oxidized teas are rich in catechins, while fully oxidized teas are rich in theaflavins and thearubigins (**Table 1**) (5).

Table 1. Flavan-3-ol Monomers and Thearubigins Content of Tea (mg/100 mL) (10)

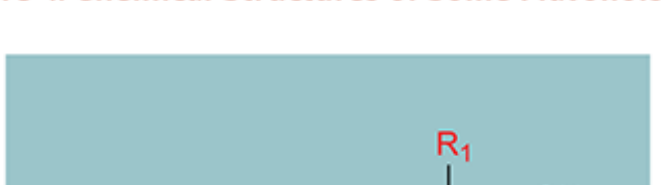
Type of Tea[1]	EC	ECG	EGC	EGCG	Thearubigins
Tea, white, brewed	-[2]	8.3	18.6	42.4	-
Tea, green, brewed	8.3	17.9	29.2	70.2	1.1
Tea, oolong, brewed	2.5	6.3	6.1	34.5	-
Tea, black, brewed	2.1	5.9	8.0	9.4	81.3

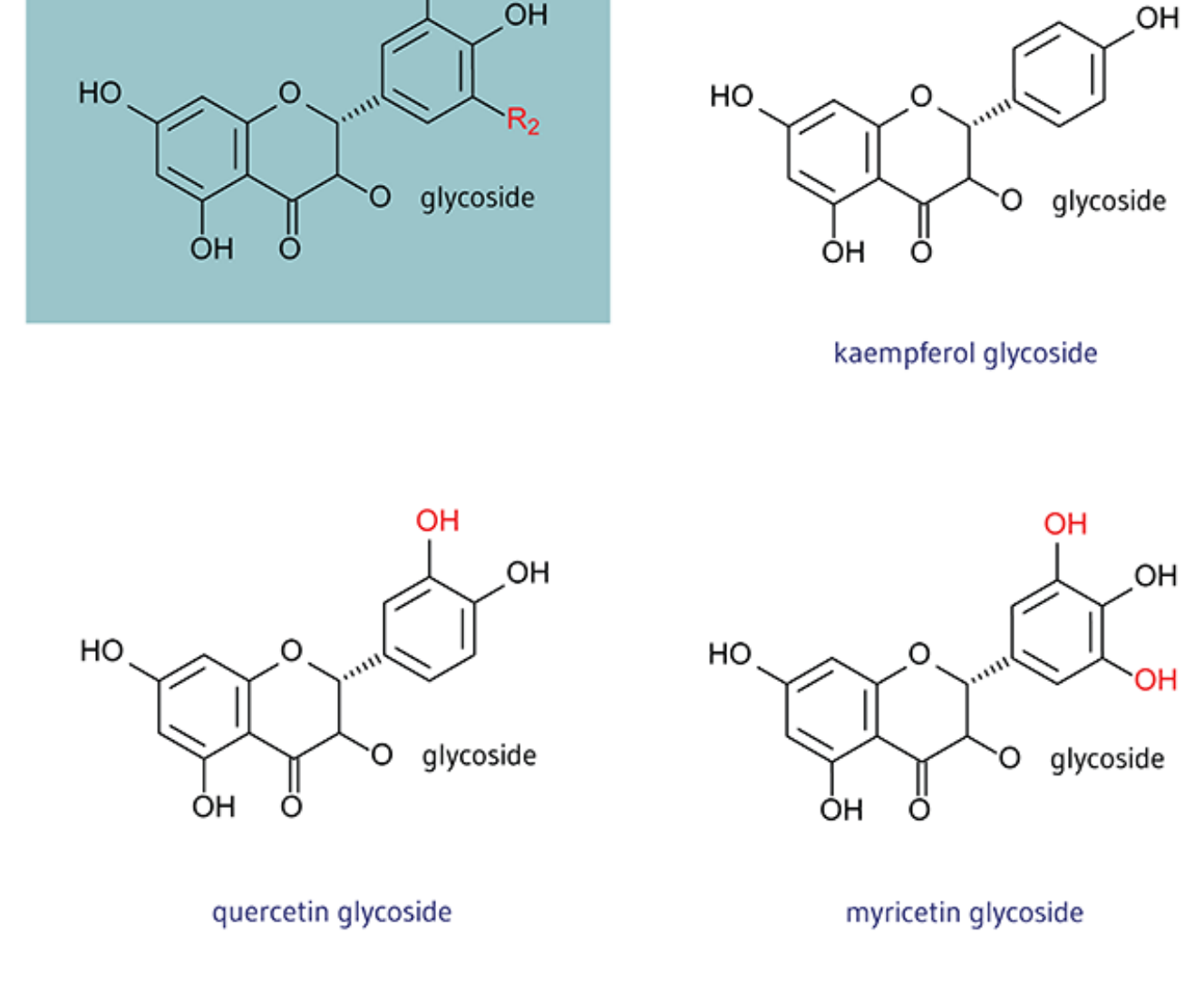
[1] 1 g of tea leaves infused in 100 mL of boiling water (1% weight/volume)

[2] The lack of a value for a particular flavonoid in a food in the database does not imply a zero value, but only that data were unavailable.

Tea is also a good source of another class of flavonoids called flavonols. Flavonols found in tea include kaempferol, quercetin, and myricetin. The flavonol content of tea is minimally affected by processing, and flavonols are present in comparable quantities in oxidized and non-oxidized teas. Unlike flavan-3-ols, flavonols are usually present in tea as glycosides, i.e., bound to a sugar molecule (**Figure 4**). Despite their poor bioavailability, flavonoids are thought to contribute substantially to the health benefits associated with daily tea consumption (10). For more detailed information, see the article on Flavonoids.

Figure 4. Chemical Structures of Some Flavonols in Tea





Caffeine

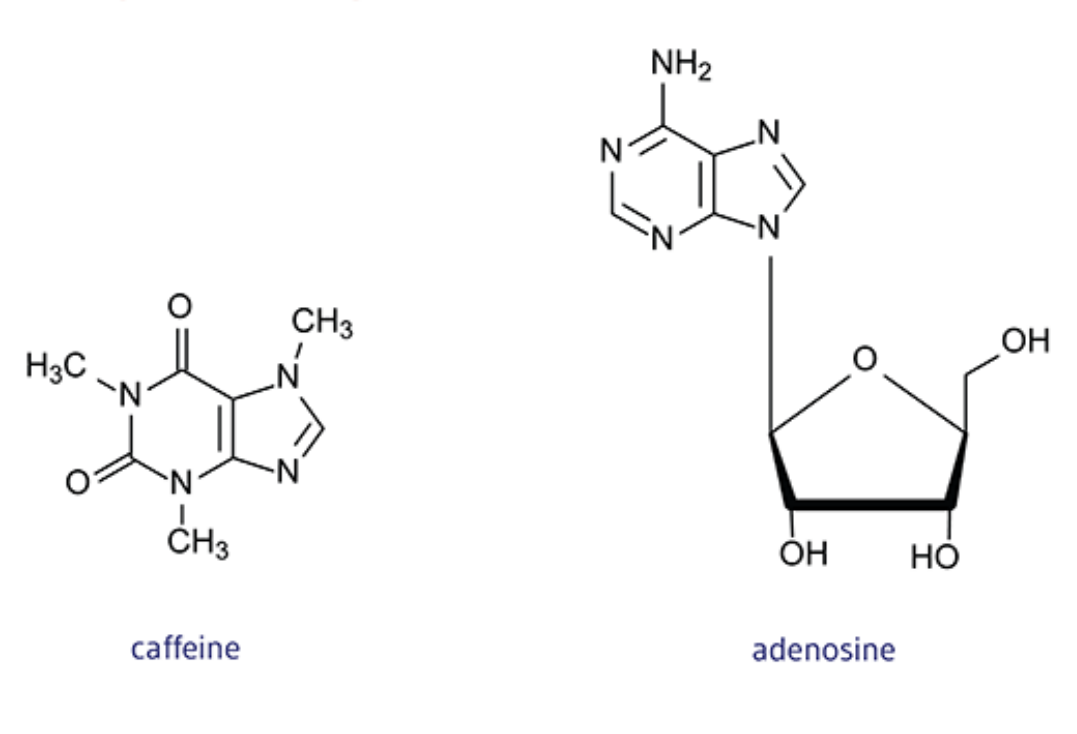
All teas contain caffeine, unless they are deliberately decaffeinated during processing. The caffeine content of different varieties of tea may vary considerably and is influenced by factors like brewing time, the amount of tea and water used for brewing, and whether the tea is loose or in teabags. In general, a mug of tea contains about half as much caffeine as a mug of coffee (11). The caffeine contents of more than 20 green and black teas prepared according to package directions are presented in **Table 2** (12). The caffeine content of oolong teas is comparable to green teas (13). There is little information on the caffeine content of white teas, since they are often grouped together with green teas (14). Buds and young tea leaves have been found to contain higher levels of caffeine than older leaves (15), suggesting that the caffeine content of some white teas may be slightly higher than that of green teas (16).

Table 2. Caffeine Content of Teas and Coffee (12, 14, 17)

Type of Tea	Caffeine (mg/L)	Caffeine (mg/8 ounces)
Green	40-234	9-63
Black	177-333	42-79
Coffee, brewed	306-553	72-130

Caffeine is a known stimulant of the central nervous system, thought to protect dopaminergic neurons by antagonizing adenosine A_{2A} receptors (**Figure 5**) (18). Because adenosine has mostly inhibitory effects in the central nervous system, the effects of adenosine antagonism by caffeine are generally stimulatory.

Figure 5. Caffeine (and Adenosine)



Fluoride

Tea plants accumulate fluoride in their leaves. In general, the oldest tea leaves contain the most fluoride (19). Most high-quality teas are made from the bud or the first two to four leaves — the youngest leaves on the plant. Fluoride levels in green, oolong, and black teas are generally comparable to those recommended for the prevention of dental caries (cavities). Thus, daily consumption of up to one liter of green, oolong, black, or pu-erh tea would be unlikely to result in fluoride intakes higher than those recommended for dental health (20, 21). The fluoride content of white tea is likely to be less than other teas, since white teas are made from the buds and youngest leaves of the tea plant. A comparative study of green, oolong, and black teas from six provinces of China found that fluoride content was inversely correlated with the quality level of tea sensory attributes (i.e., appearance, taste, flavor) (22). The fluoride content of 17 brands of green, oolong, and black teas is presented in **Table 3** (20). These values do not include the fluoride content of the water used to make the tea. For more information, see the article on Fluoride.

Table 3. Fluoride Content of Teas (21)

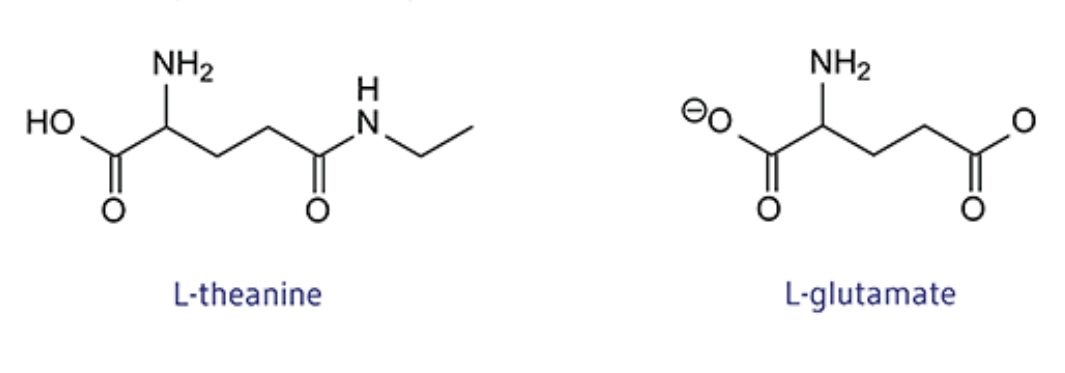
Type of Tea	Fluoride (mg/liter)[1]	Fluoride (mg/8 ounces)
Green	1.2-1.7	0.3-0.4
Oolong	0.6-1.0	0.1-0.2
Black	1.0-1.9	0.2-0.5
Pu-erh tea	0.9-1.6	0.2-0.4

[1] Fluoride in 1% weight/volume tea prepared by continuous infusion from 5 minutes (number before hyphen) to 360 minutes (number after hyphen).

L-theanine

L-theanine (also L-g-glutamylethylamide) is a non-protein amino acid that constitutes about 1%-2% (w/w) of *Camellia sinensis* dry leaves (23). L-theanine is rapidly absorbed in the small intestine and has a bioavailability close to 100% (24). L-theanine can cross the blood-brain barrier and exert neuroprotective effects (25). Because its chemical structure resembles that of glutamate, a neurotransmitter critically involved in memory, theanine may compete with glutamate for binding to glutamate receptors (**Figure 6**). This glutamate antagonism has been associated with the prevention of neuronal death by theanine after brain ischemia (reviewed in 25).

Figure 6. Theanine (and Glutamate)



Disease Prevention

Cardiovascular disease

Many epidemiological studies have considered the relationship between tea consumption and manifestations of cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke (reviewed in 26). A recent meta-analysis by Zhang et al. included the results of prospective observational studies (cohort or nested case-control studies) that examined the association between tea consumption and cardiovascular morbidity and mortality (27). The results showed that a three-cup (125 mL/cup) increase in daily tea intake was associated with a 27% lower risk of CHD (seven studies), an 18% lower risk of total stroke (eight studies), a 16% lower risk of ischemic stroke (four studies), a 21% lower risk of intracerebral hemorrhage (a type of hemorrhagic stroke), a 26% lower risk of cardiac deaths (12 studies), and a 24% lower risk of total deaths (seven studies). No associations were found between tea consumption and stroke mortality (five studies) or risk of subarachnoid hemorrhage (a subtype of stroke; two studies). Further subgroup analyses indicated that green tea consumption was specifically linked to a reduced risk of stroke, cardiac mortality, and all-cause mortality, while a lower CHD risk was associated with black tea consumption (27). Another recent meta-analysis of prospective cohort studies found that the highest versus lowest level of green tea consumption was associated with a 33% lower risk of cardiovascular mortality (five studies) and a 20% lower risk of all-cause mortality (five studies) (28). Black tea consumption was linked to a 10% reduced risk of all-cause mortality, but not specifically to cardiovascular-related mortality (28).

Tea is a major source of flavonoids in US and European diets (29, 30). The results of several epidemiological studies suggest that dietary flavonoids might influence cardiovascular health. A recent meta-analysis of 14 prospective cohort studies reported that highest versus lowest quantiles of flavonol, flavan-3-ol, flavanone, flavone, anthocyanidin, and proanthocyanidin intake were associated with modest reductions (~10%) in cardiovascular risk (31). A dose-response analysis based on the results of 13 studies in nearly 350,000 individuals and 12,445 CVD cases found a 5% risk reduction with an average 10 mg-incremental increase in daily flavonol intakes (31). It is not clear whether the antioxidant, anti-inflammatory, and/or vasodilatory properties of flavonoids are responsible for some of the cardiovascular benefits associated with tea consumption (see also the article on Flavonoids).

Intervention studies

A number of intervention trials have investigated the effects of tea consumption on markers of cardiovascular health, including biological parameters related to lipid and glucose metabolism, inflammation, blood coagulation, endothelial health, and body composition.

Metabolic markers of cardiovascular disease: Clinical trials examining the effects of green and/or black tea beverages or extracts have been relatively heterogeneous, especially regarding concentrations of active substances, duration of interventions, and included populations. Pooled analyses of mostly short-term interventions (<3 months) have suggested a reduction in total and LDL cholesterol concentrations with green tea catechin consumption, but the data regarding a potential lipid-lowering effect of black tea are inconsistent (32-34).The studies mentioned below investigated the effect of tea/tea extracts given for at least three months.

Black tea: The Tea's Effect on Atherosclerosis (TEA) pilot study in 28 older adults at increased risk for cardiovascular disease (CVD) did not find any effect of a six-month black tea consumption intervention (three glasses per day equivalent to 318 mg/day of black tea catechins) on specific biomarkers, including circulating lipoproteins, inflammation markers, homocysteine concentration, adhesion molecules, and hemostatic factors (35). Yet, in a randomized, placebo-controlled study in 47 individuals with borderline-to-moderate hypercholesterolemia, the daily consumption of 1 g of pu-erh tea (Chinese black tea) extract for three months reduced the blood concentrations of total cholesterol, LDL-cholesterol, and triglycerides (36). A three-month, placebo-controlled trial in 77 healthy subjects who drank 9 g of black tea infused in 600 mL of boiling water per day (about 740 mg/day of black tea polyphenols) had improvements in lipoprotein and triglyceride profiles, fasting serum glucose concentrations, and measures of antioxidant activities in the plasma (37). The same protocol was found to also reduce markers of oxidative stress and inflammation in the plasma of individuals at risk for CVD (38). In contrast, a recent randomized, double-blind, placebo-controlled trial in 77 regular tea drinkers (35 to 75 years old) found that the daily consumption of 429 mg of black tea polyphenols for six months had no effect on fasting blood glucose and serum lipids (39).

Green tea: Daily supplementation with a capsule containing 150 mg of green tea catechins, 75 mg of black tea theaflavins, and 150 mg of other polyphenols, for six months significantly lowered plasma LDL-cholesterol concentrations and the ratio total cholesterol:HDL in a randomized, double-blind, placebo-controlled study in 220 individuals with mild-to-moderate hypercholesterolemia (40). In a pilot study in 74 overweight/obese breast cancer survivors, the daily consumption of green tea (containing 26.7 mg of caffeine and 235.6 mg of catechins with 128.8 mg as EGCG) for six months increased HDL concentration compared to a citrus-based herbal placebo but had no effect on LDL concentration and markers of glycemic control (41). Another placebo-controlled study conducted in obese subjects with controlled hypertension found that the daily ingestion of one capsule of green tea extract (379 mg/capsule containing 208 mg of EGCG) for three months significantly lowered systolic and diastolic blood pressure and improved blood lipid profile, antioxidant status, and measures of glycemic control and inflammation (42).

Endothelial dysfunction: The vascular endothelial cells that line the inner surface of all blood vessels synthesize an enzyme, endothelial nitric oxide synthase (eNOS), which plays a critical role in maintaining cardiovascular health. Specifically, eNOS utilizes L-arginine to produce nitric oxide (NO), a compound that regulates vascular tone and blood flow by promoting the relaxation (vasodilation) of all types of blood vessels, including arteries (26). NO also regulates vascular homeostasis and protects the integrity of the endothelium by inhibiting vascular inflammation, leukocyte adhesion, platelet adhesion and aggregation, and proliferation of vascular smooth muscle cells (43). In the presence of cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, hyperglycemia), early alterations in the structure and function of the vascular endothelium are associated with the loss of normal NO-mediated endothelium-dependent vasodilation. Endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities and is considered to be an early step in the development of atherosclerosis. The measurement of brachial flow-mediated dilation (FMD) is often used as a surrogate marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (44).

Black tea: Two small controlled clinical trials found that daily consumption of 900 to 1,250 mL of black tea for four weeks significantly improved endothelium-dependent FMD in patients with coronary heart disease (45) and in patients with mildly elevated serum cholesterol concentrations (46). Improvements were noted in comparison to an equivalent amount of hot water. Incremental doses of black tea flavonoids (0, 100, 200, 400, and 800 mg/day; each dose being given for one week) have been associated with dose-dependent increases in brachial FMD in 19 healthy volunteers. Specifically, FMD values went from 7.8% at baseline (no flavonoids) to 10.3% with 800 mg/day of flavonoids (47). Of note, in this study, the ingestion of black tea flavonoids significantly lowered systolic and diastolic blood pressure in a non dose-dependent manner, while other variables, including markers of arterial stiffness, glucose metabolism, inflammation, endothelial activation, and lipid profile, remain largely unchanged (47). In a recent randomized trial, seven days of black tea consumption (450 mL/day) followed by the ingestion of two cups (300 mL) 20 minutes before an experimental ischemia-reperfusion (IR) injury procedure on healthy participants failed to prevent IR injury-associated FMD reduction. Even if tea flavonoids were able to limit the impact of IR injury on FMD — for example by counteracting the production of reactive oxygen species — the presence of caffeine in black tea (and the lack of control for it) could have confounded this effect (48).

Green tea: In a small study conducted in 14 healthy young adults (50% smokers), a significant increase in brachial FMD was reported 30 to 120 minutes after the consumption of 450 mL of green tea (6 g of green tea, including 125 mg of caffeine) compared to caffeine alone or hot water (49). Another study that compared the acute effect of black and green tea on brachial FMD in 21 postmenopausal women found a similar increase in FMD two hours after the ingestion of either tea preparation (50). Both black and green teas have been found to be equally able to increase eNOS activity and NO production in cultured endothelial cells (50, 51). Specifically, the prominent green tea catechin, EGCG, and black tea polyphenols, theaflavins and thearubigins, are thought to contribute to the protective effect of drinking tea by promoting antioxidant activity and endothelium-dependent vasodilation (51). Other flavonoids, like (-)-epicatechin and quercetin glucoside have recently failed to show an effect on FMD (and blood pressure) in hypertensive adults (52). For more information, see the article on Flavonoids.

A meta-analysis of nine human intervention studies estimated that the acute and/or short-term (up to four weeks), daily ingestion of 500 mL of tea — containing about 248 mg of flavonoids in green tea and 415 mg in black tea — significantly increased brachial FMD (53). Yet, the clinical relevance of these FMD improvements is unclear. It is also not clear whether the chronic consumption of tea might benefit vascular endothelial function and eventually lower the risk of cardiovascular disease.

Hypertension: Hypertension (high blood pressure) is a risk factor for CVD morbidity and mortality.

Black tea: A recent meta-analysis of 11 small randomized controlled trials in either healthy or at-risk individuals found a significant reduction of 2 mm Hg in systolic and 1 mm Hg in diastolic blood pressure with the daily consumption of at least 400 mL (13 oz) of black tea for one week to six months, providing a minimum of 240 mg/day of flavonoids (54). Two recent trials also reported that black tea lowered the rate of circadian variations in blood pressure at nighttime and variations after a dietary fat challenge. A six-month intervention in 76 participants from the general population (most with moderate hypertension) showed that the consumption of three cups per day of black tea, supplying a daily total of 1.29 g of polyphenols and 288 mg of caffeine, lowered the rate of nighttime blood pressure variations compared to a polyphenol-free caffeine-matched placebo (55). Two cups of black tea per day, equivalent to 300 mg of polyphenols, also limited blood pressure variations after a fat-rich meal in 19 patients with primary (idiopathic) hypertension (56). Mechanisms underlying the blood pressure-lowering properties of black tea may involve the inhibition of angiotensin-II synthesis by flavonoids (see below).

Green tea: Several recent meta-analyses of randomized controlled trials indicated that the consumption of green tea or green tea extracts could significantly lower blood pressure (57-60). In one of them, the pooled analysis of 13 trials in 1,367 subjects found a 2.0 mm Hg reduction in systolic blood pressure and a 1.9 mm Hg reduction in diastolic blood pressure with green tea polyphenols (208 mg/day-1,207 mg/day) for a median period of 12 weeks (60). Subgroup analyses suggested greater blood pressure lowering effect with polyphenol intake levels lower than 582.8 mg/day and with adjustment for the confounding effect of caffeine. Another meta-analysis included randomized controlled trials that specifically explored the effect of green tea or green tea extracts on blood pressure in overweight or obese subjects. The pooled analysis of 14 trials showed significant reductions of 1.4 mm Hg in systolic blood pressure and 1.3 mm Hg in diastolic blood pressure (58). The anti-hypertensive effect of green tea may be mediated by a number of mechanisms. For example, pharmacological concentrations of several catechins have been shown to inhibit the activity of a key regulator of arterial blood pressure, angiotensin-converting enzyme (ACE), *in vitro* (61). ACE catalyzes the conversion of angiotensin-I into angiotensin-II, a potent inducer of vasoconstriction. In addition, studies in rats showed that chronic treatment with epicatechin prevented salt-induced hypertension, partly through inhibition of endothelin-1 expression and NADPH oxidase (NOX) activity (62). Other potential benefits of green tea consumption, including improvements in blood lipid profile, insulin sensitivity, and endothelial function, may also contribute to its blood pressure-lowering effects.

Type 2 diabetes mellitus

Impaired glucose tolerance in patients with prediabetes is often associated with loss of insulin sensitivity, impaired lipid metabolism, low-grade inflammation, and endothelial dysfunction (63). Without changes in lifestyle behavior (especially regarding dietary habits and physical activity), individuals with prediabetes will eventually progress to develop overt type 2 diabetes mellitus (64).

In this context, the association between tea consumption and risk of type 2 diabetes has been examined in a recent European, multicenter, nested case-control study — the "EPIC-InterAct" project — that included 16,835 diabetes-free participants and 12,043 individuals with diabetes (65). The results showed that tea consumption was inversely associated with diabetes incidence. The consumption of four cups per day rather than none was found to be associated with a 16% lower risk of diabetes (65). Of note, in a meta-analysis of 15 prospective cohort studies, including the EPIC-InterAct study, an incremental increase of two cups per day in tea consumption was found to be associated with an estimated 4.6% risk reduction (66). The EPIC-InterAct study also found that participants in the highest quintile (>608.1 mg/day) of total flavonoid intake had a 10% lower risk of diabetes than those in the lowest quintile (<178.2 mg/day) (67). Specifically, the risk of diabetes was inversely correlated with the consumption of flavan-3-ols (catechins, proanthocyanidins, and theaflavins) and flavonols (67, 68). The intakes of other flavonoid subclasses that are less abundant in tea, namely anthocyanidins, flavanones, flavones, and isoflavones, were not associated with a reduced risk of diabetes (67).

Recent meta-analyses of randomized controlled trials that examined the possible health benefits of green tea catechins on glucose metabolism have provided conflicting results. A meta-analysis of seven trials in prediabetic and diabetic patients found no effect of green tea or green tea extracts on fasting plasma glucose, fasting serum insulin, or measures of glycemic control (HbA1c) and insulin sensitivity (HOMA-IR) (69). Conversely, another meta-analysis of 17 trials in prediabetic, diabetic, or overweight/obese subjects found that administration of green tea extracts for 4 to 16 weeks improved fasting plasma glucose and HbA1c levels (70). The effect on fasting glucose was observed only with high doses of catechins (≥457 mg/day) and when the confounding effect of caffeine was removed. However, a third meta-analysis of 25 trials found that ingestion of green tea extracts for at least two weeks could lower fasting blood glucose in both the presence or absence of caffeine (71).

Overweight and obesity

A recent meta-analysis of five small, randomized controlled trials (<100 participants per study) found that regular consumption of green or pu-erh tea extracts reduced body weight and body mass index (BMI) in overweight/obese participants with metabolic syndrome (72). The influence of green tea on body composition may be attributed to the regulation of appetite, fat absorption, fatty acid oxidation, and thermogenesis by catechins and caffeine (73). Yet, studies in overweight/obese people who are otherwise healthy have provided mixed results (reviewed in 74). Intervention studies in Caucasian populations have shown a less favorable effect of green tea catechins on body weight and energy expenditure compared to those conducted in Asian subjects. These discrepancies suggested that differences in genetic background, body composition, and dietary habits (including caffeine consumption) might interfere with the possible anti-obesity effect of green tea consumption. Large-scale, intervention trials that control for energy intake and physical activity are needed to determine if tea or tea extracts promote weight loss or improve weight maintenance in different populations with obesity and/or metabolic syndrome (74).

Cancer

Tea and tea constituents have been found to have cancer preventive activities in a variety of animal models of cancer, such as cancer of lung, mouth, esophagus, stomach, colon, and prostate (75). However, the results of epidemiological studies in humans have been mostly inconclusive.

Breast cancer

An early meta-analysis of prospective cohort studies had reported that black tea intake (five cohorts) — but not green tea (three cohorts) — was associated with a 15% higher risk of breast cancer (76). The relationship between tea consumption and breast cancer has been recently examined in the Swedish Women's Lifestyle and Health prospective cohort Study (WLHS), which followed 42,099 women for 20 years and documented 1,395 breast cancer cases (77). The results indicated a 14% higher risk of breast cancer with each cup (200 mL) of tea consumed daily. The risk was specifically increased in postmenopausal women rather than in premenopausal women. Similarly, in a recent case-control study in Chinese women in Hong Kong, regular tea consumption was inversely correlated with breast cancer risk in premenopausal women but associated with an increased risk in postmenopausal women (78). The risk associated with consuming tea was also significantly higher for estrogen- and progesterone-receptor-positive (ER+/PR+) breast cancer type in the Swedish cohort, while the highest risk was found in women with ER-negative tumors in the Chinese study (77, 78). Yet, in the European Prospective Investigation into Nutrition and Cancer Study (EPIC) in 335,060 women followed for 11 years (10,198 incidental breast cancer cases), tea intake was not associated with breast cancer overall or when the data were analyzed for menopausal status or breast cancer type (79). The most recent meta-analysis of prospective cohort studies found no association between consumption of green or black tea and breast cancer (80). Thus, current epidemiological evidence does not suggest a benefit of tea in breast cancer prevention despite promising data from cultured cells and rodent models (81).

However, some observational studies found that consumption of certain subclasses of flavonoids might have the potential to reduce the incidence of breast cancer in postmenopausal women (82). Recently, the effects of decaffeinated green tea extracts on biomarkers of breast cancer risk were examined in the Minnesota Green Tea Trial (MGTT) in 1,075 high-risk postmenopausal women randomized to receive the equivalent of four 8-ounce mugs/day (960 mL/day) in green tea extracts (1,315±116 mg/day of catechins) or a placebo for one year (83). The results have yet to be published.

Mouth, throat, and esophageal cancers

In the large, prospective NIH-AARP Diet and Health study (1995-2006) in 481,563 US adults, 1,305 cases of oral (392), pharyngeal (178), laryngeal (307), and esophageal (428) cancers have been identified during the follow-up period (84). The highest versus lowest level of tea intake (≥1 cup/day vs. non-consumption) was correlated with a 63% lower risk of pharyngeal cancer but with no other above-cited cancer types (84). Observational studies do not currently provide clear evidence for an association between tea consumption and laryngeal (85) or esophageal (86) cancers. In the case of esophageal cancer, the consumption of high-temperature beverages (including very hot tea) might even damage the epithelium and increase the risk of cancer (87). High temperature may act as a confounding factor that complicates the interaction between tea consumption and esophageal cancer (88). In 2009, a phase II, randomized, double-blind trial was conducted in 41 patients with high-risk oral premalignant lesions (OPLs). Participants were randomly assigned to orally receive 0.5, 0.75, or 1 g of green tea extract per m^2 (body surface area) or a placebo, thrice a day for three months. While the results suggested that OPLs might be clinically responsive to green tea extract treatment, larger trial populations are needed to confirm these preliminary data (89).

Gastric cancer

Several prospective cohort studies reported no association between tea consumption and risk of gastric cancer (90-92), including the US NIH-AARP Diet and Health study (84). Tea consumption also failed to predict gastric cancer cases in the EPIC study, which followed 477,312 participants and identified 683 cases during a median 11.6 years of follow-up (93). Yet, a decreased risk of intestinal type gastric cancer was observed in women in the highest versus lowest quartile of tea consumption (≥475 mL/day vs. ≤21 mL/day). Interestingly, women (but not men) in the highest versus lowest quartile of flavonol, flavanol, theaflavin, or total flavonoid intakes had a significantly reduced risk of developing gastric cancer (94). A pooled analysis of six Japanese cohort studies, including 219,080 total participants and 3,577 cases, found an inverse association between green tea consumption and gastric cancer in women but not in men: daily consumption of at least five cups of tea was associated with a 21% lower risk of gastric cancer in women compared to low intakes (<1 cup/day) (95).

Gynecologic cancers

Meta-analyses of case-control studies have found a significant 34% reduction in risk of ovarian cancer for highest versus lowest intake of green tea (four studies) (96), but no association was observed for black tea (six studies) (97). Yet, a meta-analysis of six prospective studies showed an inverse relationship between black tea consumption and ovarian cancer (98). A recent analysis of the Nurses' Health Studies (NHS I and II) showed a 31% lower risk of ovarian cancer in women consuming at least 1 cup/day compared to rare/non-black tea drinkers (99). In a prospective study in 244 women diagnosed with ovarian cancer and followed for over three years, green tea consumption was associated with a mean survival time greater for consumers (5.39 years) than for non-consumers (4.19 years) (100). However, in a single-arm, phase II trial in 16 women in complete remission from advanced stage ovarian cancer, the daily intake of 500 mL of green tea (containing 319.8 mg of EGCG) failed to effectively prevent cancer recurrence within the 18-month follow-up period (101). Further, a recent systematic review and meta-analysis of observational studies suggested a possible benefit of green tea — but not black tea — for endometrial cancer (102).

Additional studies have examined the association between tea consumption and risk of lung, prostate, liver, or colorectal cancer in humans, providing mixed results (reviewed in 103).

Bone health and osteoporosis

The etiology of osteoporosis is complex, involving factors such as aging, decreased sex hormones, inadequate nutrition, physical inactivity, genetic predisposition, as well as socioeconomic determinants. Tea bioactive components, including flavonoids, caffeine, and fluoride, have the potential to influence health and the risk of osteoporosis and fracture (104, 105). A small prospective study in 164 elderly women found that consumption of tea limited the age-related loss in total hip bone mineral density (BMD) over a four-year follow-up period (106). Also, in a six-month randomized, placebo-controlled trial in 171 postmenopausal women with osteopenia, the daily consumption of green tea catechins (500 mg) alone or combined with Tai Chi exercise (3 hours/week) improved bone turnover by stimulating bone formation (107).

Hip fracture is one of the most serious consequences of osteoporosis. A recent prospective study in 1,188 elderly women (mean age, 80 years) followed for 10 years found that participants in the highest versus lowest tertile of tea consumption (≥3 cups/day vs. ≤1 cup/week) had a 30% lower risk of any osteoporotic fracture. However, no interaction was found when the analysis was conducted on major fractures (hip, spine, humerus, and wrist) or hip fractures only (108). Yet, a meta-analysis based on 147,488 individuals from 11 observational studies published between 1990 and 2010 suggested that the consumption of 1-4 cups/day was associated with a significantly lower risk of hip fracture (109). The results of another recent meta-analysis of mostly case-control studies did not suggest any interaction between tea consumption and risk of any fracture or hip fracture (110). Additional studies are required to determine whether tea consumption affects the development of osteoporosis or the risk of osteoporotic fracture in a meaningful way.

Dental health

The cross-sectional analysis of the Ohsaki prospective cohort study that included data from 25,078 Japanese participants found an inverse association between the daily consumption of at least one cup of tea and the risk of tooth loss (111). Specifically, the risk of tooth loss was 11% lower in women and 23% lower in men who consumed at least five cups per day of tea compared to those drinking less than one cup per day. An earlier cross-sectional study of more than 6,000 14-year old children in the UK found that those who drank tea had significantly fewer dental caries than coffee drinkers; results were independent of the amount of beverage consumed or whether sugar was added (112). Although tea is a good source of fluoride — a recognized anticaries agent — both flavonoids and tannins in tea have been shown to have antimicrobial properties (reviewed in 113). Oral bacteria like *Streptococcus mutans* and *Porphyromonas gingivalis* have been associated with plaque formation, dental caries, and periodontal (gum) diseases. Untreated caries and gum inflammation can lead to severe pain, local infection, tooth loss or extraction, nutritional problems, and serious systemic infections in susceptible individuals. A pilot study in 25 adults suggested that mouthwash with a 2% green tea solution could lower acidity level and *Streptococcus mutans* count in saliva and plaque and improve measures of gum bleeding after exposure to sugar (114). A small, randomized study in 66 young volunteers (12-18 years old) also reported a significant antibacterial effect of a mouth rinse made with pulverized tea leaves compared to a placebo solution (115). Recent randomized, double-blind, controlled studies demonstrated further that tea extract-containing mouthwashes could benefit dental health and offer a possible alternative to current chlorhexidine- and fluoride-containing rinsing solutions (116-118). Finally, the incorporation of tea extract in toothpastes was found to be as effective — if not better — than regular pastes (containing fluoride and triclosan) to reduce dental plaque and gum inflammation in patients with mild to moderate periodontitis (119).

For more information on dental caries, see the article on Fluoride.

Kidney stones

The formation of kidney stones, usually composed of calcium oxalate or calcium phosphate, is a common condition that affects 7% of US women and 11% of US men during their lifetime (120). A pooled analysis of three ongoing prospective cohort studies — the Health Professionals Follow-up Study and the Nurses' Health Studies I and II, including a total of 194,095 participants — found that the risk of developing symptomatic kidney stones was 11% lower in individuals consuming at least one 8-ounce mug of tea per day compared to those consuming less than one cup per week (121). High fluid intake, including tea intake, is generally considered the most effective and economical means of preventing kidney stones (122). However, the finding that black tea may contain high amounts of oxalate (48 to 92 mg/100 mL) suggested that black tea consumption may increase urinary oxalate concentrations, a risk factor for calcium oxalate stone formation (123). The Academy of Nutrition and Dietetics recommends that kidney stone patients restrict oxalate intake to 40 mg/day-50 mg/day, and some experts advise those with a history of calcium oxalate stones to limit the consumption of oxalate-rich food, including black (but not green) tea (123, 124). Yet, recent studies have reported amounts of oxalate in different samples of green teas (0.8 to 14 mg/100 mL) (125) and black teas (1 to 2.6 mg/100 mL) (126, 127) much lower than previously published, suggesting that tea consumption would not increase kidney stone incidence or recurrence.

Mood

The term "mood" refers to an emotional state of mind that includes aspects like contentedness, relaxation, alertness, energy, and relief from depression, anxiety, and feelings of guilt and failure (128). Clinical depression is described as a mood disorder. An analysis of the NIH-AARP Diet and Health Study (1995-2006) in 263,923 participants — of which 11,311 self-reported depression — found that consumption of decaffeinated (but not caffeinated) hot tea was associated with an increased risk for depression (129). However, smaller cohort studies had previously recorded significantly less depressive symptoms in participants with higher versus lower intakes of tea (130, 131).

Tea consumption may have short-term effects on mood. In a recent cross-sectional study in 95 university staff members, consumption of tea recorded during 10 working days was associated with self reports of feeling less tired and performing better at work (132). Tea was also found to increase the positive valence of mood immediately after consumption in a small randomized controlled study in 150 participants (133).

Cognitive function

Cognitive function includes the domains of attention, memory, processing speed, and executive function, which decline gradually with increasing age.

Cognitive performance

A few studies investigated whether tea consumption was associated with cognitive benefits, especially in the domain of attention (reviewed in 134). Two cross-over, randomized, double-blind, placebo-controlled studies evaluated the effects of two servings of black tea over the course of 60 min (study 1; 26 volunteers) or three servings of black tea over the course of 90 min (study 2; 32 volunteers) on measures of attention and alertness (135). Both studies reported improved performance on objective attention tests and self-reported alertness with black tea compared to placebo. In a small open-label study, 19 participants were asked to consume either black tea (with/without caffeine), coffee (with caffeine), or water (with/without caffeine) before undergoing a battery of psychometric tests (136). Most of the improvements in cognitive function (measured with the Critical Flicker Fusion Threshold [CFFT] task) and subjective alertness were attributed to caffeine in the beverages. In addition, CFFT task scores were greater after consumption of caffeinated tea compared to caffeinated water (136). In a follow-up study, caffeinated tea outperformed caffeinated coffee in the CFFT test, suggesting that tea ingredients other than caffeine might have acute effects on cognitive function (137). A recent meta-analysis of small, randomized controlled trials (<50 participants/trial) that measured the acute effect of L-theanine (36 mg-250 mg) with or without caffeine (40 mg-250 mg) suggested an increase in alertness and attention-switching accuracy but no change regarding other parameters, such as calmness, contentedness, or anxiety (138).

Cognitive decline

The cross-sectional data analysis of 2,501 participants (≥55 years old) in the Singapore Longitudinal Ageing Study (SLAS) indicated that higher intakes of tea correlated with better global cognitive function, as assessed by Mini-Mental State Examination (MMSE) scores (139). Conversely, lower levels of tea consumption were associated with a higher prevalence of cognitive impairments, defined as MMSE scores ≤23. Similar observations have been reported in several other cross-sectional studies (140-143). In the SLAS study, the follow-up of 1,438 cognitively healthy people for one to two years showed that the risk of cognitive decline (defined as a drop of ≥1 point in the MMSE score) was up to 43% lower in tea drinkers compared to non-drinkers (139). Further research in 716 SLAS participants (mean age, 64.5 years) with normal cognitive function confirmed that those consuming tea scored higher in the MMSE global cognition test than non-consumers. Tea consumption was also correlated with higher cognitive test scores regarding memory, executive function, and information-processing speed (144). Tea consumption was also modestly associated with a reduced risk of cognitive decline in 2,722 women (but not in men) followed for a median 7.9 years in the US population-based Cardiovascular Health Study, despite a much lower frequency of tea consumption (up to 5 cups/week) than that observed in the SLAS (over 10 cups/day) (145). In a prospective cohort study in Japanese older people (>60 years old) followed for nearly five years, daily green tea consumers were shown to have lower risks of mild cognitive impairments (MCI) and dementia compared to non-consumers (146). In a recent pilot trial, the consumption of green tea extracts (2 g/day, of which 227 mg of catechins and 42 mg of theanine) for three months resulted in higher MMSE scores (compared to baseline) due to improved short-term memory scores in 12 elderly nursing home residents (ages, 70 to 98 years) with symptoms from MCI to severe dementia (147).

Long-term, large randomized controlled trials are needed to establish whether tea or its bioactive components could limit cognitive decline and/or improve cognitive dysfunction in older individuals.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by the selective death of dopaminergic brain cells in the substantia nigra. PD is estimated to affect 0.5%-4% of older people (≥65 years old) worldwide (148). A retrospective study in 279 subjects with PD suggested that the onset of motor symptoms in those drinking more than 3 cups/day of tea was delayed by several years compared to nondrinkers (149); yet, after disease onset, a similar rate of disease progression was observed among tea drinkers and non-drinkers (150). A meta-analysis of eight case-control studies, including 4,250 controls and 1,418 PD cases, found a 15% reduced risk of PD with higher versus lower intake of tea (151). Another meta-analysis of four case-control studies and four prospective cohort studies published between 1999 and 2012 indicated that individuals in the highest category of tea consumption had a 37% lower risk of PD compared to those in the lowest category (152). The authors estimated that each 2 cups/day-increase in tea consumption was associated with a 26% lower risk of developing PD (152). If a protective effect of tea consumption can be further demonstrated, several bioactive compounds, especially caffeine (153) and flavonoids (154), could be responsible for the tea benefits in PD prevention.

Safety

Adverse effects

Tea

Tea is generally considered to be safe, even in large amounts. However, two cases of hypokalemia (abnormally low serum potassium concentrations) in the elderly have been attributed to excessive consumption of black and oolong tea (3 L/day-14 L/day) (155, 156). Hypokalemia is a potentially life-threatening condition that has been associated with caffeine toxicity (157, 158). Case reports of stomach cramps (159), kidney stones (160), and skeletal fluorosis (161-163) due to excessive tea consumption have also been published.

Tea extracts

In clinical trials employing caffeinated green tea extracts, cancer patients who took 6 g/day, in three to six divided doses, experienced mild-to-moderate gastrointestinal side effects, including nausea, vomiting, abdominal pain, and diarrhea (164, 165). Central nervous system symptoms, including agitation, restlessness, insomnia, tremors, dizziness, and confusion, have also been reported. In one case, confusion was severe enough to require hospitalization (164). In a systematic review published in 2008, the US Pharmacopeia (USP) Dietary Supplement Information Expert Committee identified 34 adverse event reports implicating the use of green tea extract products (containing 25%-97% of polyphenols) as the likely cause of liver damage (hepatotoxicity) in humans (166). Nineteen additional cases of hepatotoxicity associated with the consumption of herbal products containing green tea have been reported for the period 2008-2015 (167). In a four-week clinical trial that assessed the safety of decaffeinated green tea extracts (800 mg/day of EGCG) in healthy individuals, a few of the participants reported mild nausea, stomach upset, dizziness, or muscle pain (168). In the Minnesota Green Tea Trial (MGTT), 1,075 postmenopausal women were randomized to receive green tea extracts (1,315±116 mg/day of catechins; the equivalent of four 8-ounce mugs of brewed decaffeinated green tea) or a placebo for one year. The total number of adverse events and the number of serious adverse events were not different between the treatment and placebo groups (169). However, the use of green tea extracts was directly associated with abnormally high liver enzyme levels in 7 out of the 12 women who experienced serious adverse events. Also, the incidence of nausea was twice as high in the green tea arm as in the placebo group (169).

Pregnancy and lactation

The safety of tea extracts or supplements for pregnant or breast-feeding women has not been established. Some organizations, like the American College of Obstetricians and Gynecologists, suggest to limit caffeine consumption during pregnancy to less than 200 mg/day (170), because higher caffeine intakes have been associated with increased risk of miscarriage and low birth weight in some epidemiological studies (171, 172).

Drug interactions

Green tea

Excessive green tea consumption may decrease the therapeutic effects of the anticoagulant, warfarin (Coumadin, Jantoven). Such an effect was documented in only one patient who began drinking one-half gallon to one gallon of green tea daily (173). It is probably not necessary for people on warfarin therapy to avoid green tea entirely; however, large quantities of green tea may increase the risk of bleeding in warfarin-treated patients (174). Green tea extracts may also reduce the efficacy or increase the toxicity of at least two other cardiovascular drugs, namely simvastatin (Zocor) and nadolol (Corgard) (175). Preclinical studies suggested that green tea extracts may interfere with drug metabolism by affecting the activity of cytochrome P450 3A4 (CYP3A4), which catalyzes the metabolism of about one-half of all marketed drugs in the US and Canada (176). Additional information on drug interactions is available in the article on Flavonoids.

Caffeine

A number of drugs can impair the metabolism of caffeine, increasing the potential for adverse effects from caffeine (177). Such drugs include cimetidine (Tagamet), disulfiram (Antabuse), estrogens, fluoroquinolone antibiotics (e.g., ciprofloxacin, enoxacin, norfloxacin), fluconazole (Diflucan), fluvoxamine (Luvox), mexiletine (Mexitil), riluzole (Rilutek), terbinafine (Lamisil), and verapamil (Calan). High caffeine intakes may increase the risk of toxicity of some drugs, including albuterol (Ventolin), metaproterenol (Alupent), clozapine (Clozaril), ephedrine, stimulant drugs (e.g., epinephrine), monoamine oxidase inhibitors, phenylpropanolamine, and theophylline. High caffeine intakes may also reduce the bioavailability and/or the efficacy of drugs like carbamazepine, valproate, dipyridamole (Persantine), pentobarbital (Nembutal), and phenobarbital (Luminal). Abrupt caffeine withdrawal has been found to increase serum lithium levels in people taking lithium, potentially increasing the risk of lithium toxicity.

Nutrient interactions

Iron

Flavonoids in tea can bind nonheme iron, inhibiting its intestinal absorption (178, 179). Nonheme iron is the principal form of iron in plant foods, dairy products, and iron supplements. The consumption of one cup of tea with a meal has been found to decrease the absorption of nonheme iron in that meal by about 70% (180, 181). Flavonoids can also inhibit intestinal heme iron absorption (182). Interestingly, ascorbic acid (vitamin C) greatly enhances the absorption of iron and is able to counteract the inhibitory effect of flavonoids on nonheme and heme iron absorption (179, 182, 183). To maximize iron absorption from a meal or iron supplements, subjects with poor iron status should not consumed tea at the same time (184). In addition, healthy individuals at no risk of iron deficiency do not need to restrict their consumption of tea (184, 185).

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Alcoholic Beverages

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Summary

- Observational studies have consistently found that moderate alcohol consumption (no more than two alcoholic drinks/day for men and no more than one alcoholic drink/day for women) is associated with a decreased risk of cardiovascular and all-cause mortality. *(More information)*
- Moderate alcohol consumption is associated with lowered risks of coronary heart disease (CHD) and ischemic stroke. *(More information)*
- Evidence from observational studies suggests that moderate alcohol intake may be associated with reduced risk of type 2 diabetes, dementia, and gallstones, as well as with improved bone mineral density. *(More information)*
- Even moderate alcohol consumption may increase the risk of female breast cancer, alcohol-related birth defects, and progression to heavy alcohol consumption in some people. *(More information)*
- Heavy alcohol consumption is associated with increased risks of hypertension, stroke, heart rhythm disturbances, dementia, accidents, injury, violence, and damage to the heart, liver, and pancreas. *(More information)*
- Heavy alcohol consumption is associated with increased risk of many cancers, including cancers of the mouth, pharynx, larynx, esophagus, liver, breast, colon and rectum. The combined use of alcohol and tobacco greatly increases the risk of oral and esophageal cancers. *(More information)*
- Those who consume more than minimal amounts of alcohol should make sure they also consume adequate folate by taking a daily multivitamin that provides 400 μg of folic acid. *(More information)*
- There is consensus that the health risks of moderate alcohol consumption outweigh the health benefits for some people. People who should abstain from alcohol include (1, 2): children and adolescents; pregnant women and women who may become pregnant; anyone who has trouble limiting his or her alcohol consumption to moderate levels, particularly recovering alcoholics and those with a family history of alcoholism or alcohol problems; and anyone with chronic liver disease or alcohol-related disease or organ damage.
- Anyone planning to drive, operate heavy machinery, or perform other potentially hazardous activities requiring coordination and skill should not consume alcohol.
- People who would benefit from individualized advice regarding potential health risks and benefits of moderate alcohol consumption include: anyone taking medications (over-the-counter or prescription) with the potential for adverse interactions with alcohol; and anyone with a personal or family history (e.g., parent or sibling) of breast cancer, coronary heart disease, or other conditions related positively or inversely to moderate drinking.

Introduction

While excessive alcohol consumption has been linked to a number of serious health and social problems, observational studies have associated moderate alcohol consumption with some important health benefits. The relationship between alcohol consumption and mortality is often described as J-shaped, meaning that when graphed from alcohol abstinence on the left to heavy drinking on the right, light-to-moderate alcohol consumption (≤2 drinks/day) is associated with lower rates of mortality — mostly from cardiovascular disease — than abstention, while heavy alcohol consumption (>3-4 drinks/day) is associated with higher rates of mortality from a number of causes (3-5). Because the consumption of alcohol can be viewed as a "double-edged sword," individual decisions regarding alcohol use should take into consideration scientific evidence regarding potential health benefits and risks, as well as personal and family histories of health problems and addictions.

It is important to note the data on alcohol-disease relationships come from only observational studies, not randomized controlled trials, and observational data cannot establish causation. In observational research, potential confounding variables should be adequately adjusted for using statistical techniques. For instance, nondrinkers have been shown to differ from those who consume alcohol in ways that might affect the disease outcome of interest (6). Even when controlling for many potential confounders, residual confounding may still occur.

Definitions (7)

Standard alcoholic drink (8)

A standard alcoholic drink contains approximately 14 grams of alcohol, which is equivalent to 12 ounces of beer (~5% alcohol), 8.5 ounces of malt liquor (~9% alcohol), 5 ounces of wine (~12% alcohol), 3.5 ounces of fortified wine (e.g., sherry or port), or 1.5 ounces of liquor (distilled spirits; ~40% alcohol).

Moderate alcohol consumption

- **Men**: No more than two standard alcoholic drinks/day (9)
- **Women**: No more than one standard alcoholic drink/day* (9)
- There is consensus that distributing total weekly alcohol intake evenly to most days is the healthiest drinking pattern.

Heavy alcohol consumption (8)

- **Men**: More than 14 standard alcoholic drinks/week or more than 4 standard alcoholic drinks in a day
- **Women**: More than 7 standard alcoholic drinks/week or more than 3 standard alcoholic drinks in a day*

*In addition to weighing less, on average, women absorb and metabolize alcohol differently than men. In general, women have less body water than men of similar body weight, so women achieve higher blood alcohol concentrations after drinking equivalent amounts of alcohol (10). Women also appear to be more vulnerable to adverse health effects of heavy drinking than men. Thus, most definitions of "moderate" or "heavy" drinking offer a lower threshold for women.

Potential Health Benefits of Moderate Alcohol Consumption

Mortality

Data from observational studies have shown that light-to-moderate alcohol consumption (≤1 drink/day for women and ≤2 drinks/day for men) is protective against all-cause mortality (4, 11-15). As mentioned above, a J-shaped relationship is apparent when all-cause mortality is plotted against alcohol consumption (alcohol abstinence on the left and heavy drinking on the right of the x-axis) (4, 16). In other words, those who drink moderately have the lowest risk of total mortality when compared to nondrinkers and heavy drinkers, and heavy drinkers have the highest risk of mortality.

The association of reduced mortality with moderate alcohol consumption is largely attributed to a decrease in cardiovascular mortality (14, 16-18), especially from coronary heart disease (see Cardiovascular disease below). However, concern has been raised that some earlier observational studies have misclassified former drinkers in the lifetime abstention group (i.e., the referent group), but most recent studies have not supported such a 'misclassification hypothesis' (15, 16, 19).

Cardiovascular disease

Coronary heart disease

Over the past four decades, the most consistent evidence of a health benefit associated with moderate alcohol consumption has been a significant reduction in the risk of coronary heart disease (CHD) — a finding confirmed by a large number of epidemiological studies. When the results of 28 prospective cohort studies were combined in a meta-analysis, adults who consumed an average of 25 grams/day of alcohol (the amount in two standard alcoholic drinks) had a risk of CHD that was 20% lower than adults who did not consume alcohol (20). More recent data from two large prospective cohort studies conducted in the US suggest that the magnitude of CHD risk reduction associated with moderate alcohol consumption may be closer to 30%. In a 12-year study of more than 38,000 male health professionals, those who consumed alcohol at least 3-4 times weekly had a risk of myocardial infarction (heart attack) that was 32% lower than men who drank alcohol less than once weekly (21). Similarly, in a 20-year study of more than 120,000 men and women, those who reported consuming 1-2 alcoholic drinks daily had a risk of death from CHD that was 30% lower than those who did not drink alcohol (22). A 2011 systematic review and meta-analysis of 29 studies found that alcohol consumption was associated with a 29% reduced risk of CHD compared to abstention; intakes of 2.5 to 60.0 grams/day of alcohol were associated with a lower risk of CHD (16).

How does alcohol consumption reduce CHD risk? The development of CHD is characterized by the formation of cholesterol-laden plaque in the arteries (atherosclerosis), vascular inflammation, and clot formation (23). Numerous small, randomized trials have examined the effect of daily alcohol consumption on markers of CHD risk, consistently finding that moderate alcohol consumption significantly increases concentrations of high-density lipoprotein (HDL)-cholesterol — the 'good cholesterol' (24, 25). HDLs transport cholesterol from tissues, including arterial walls, back to the liver for elimination or recycling. In addition to increasing HDL levels, moderate alcohol consumption has been shown to increase apolipoprotein A1, a major component of circulating HDL (25). Higher levels of high-density lipoprotein (HDL)-cholesterol have been associated with reductions in CHD risk (26).

Alcohol may also have anti-thrombotic properties. Clot formation is the result of complex interactions between factors that promote coagulation and factors that inhibit coagulation or promote the dissolution of clots. Several randomized trials have found that moderate alcohol consumption decreases serum levels of fibrinogen, a protein that promotes clot formation (25) and increases serum levels of an enzyme that helps dissolve clots (tissue type plasminogen activator) (24).

Further, moderate alcohol consumption may have an anti-inflammatory effect since serum levels of C-reactive protein (CRP), a marker of systemic inflammation and sensitive predictor of CHD risk, are lower in people who drink moderately than those who abstain from alcohol (27-32). Moderate alcohol consumption has also been associated with improvements in adiponectin levels (25), insulin sensitivity (see Type 2 diabetes mellitus below), abdominal obesity (33), and endothelial function (34).

Does the type of alcohol consumed (wine, beer, or liquor) affect CHD risk? Significant reductions in CHD risk have been associated with moderate consumption of wine, beer, and liquor. However, the "French Paradox" — the observation that mortality from CHD is relatively low in France despite relatively high levels of dietary saturated fat and cigarette smoking — led to the idea that regular consumption of red wine might provide additional protection from CHD (35, 36). Red wine contains the phenolic compound resveratrol — although usually at variable and low concentrations (see the article on Resveratrol) — as well as flavonoids like procyanidins; these compounds could provide additional cardiovascular benefits beyond those associated with ethanol. Beer also contains polyphenolic compounds that might confer some cardioprotection (37).

Some large prospective cohort studies have found wine drinkers to be at lower risk of CHD than beer or liquor drinkers (22, 38-40), but others have found no difference (21, 41, 42). Moreover, some studies have observed a decreased risk of myocardial infarction or CHD in predominantly beer-drinking populations in the Czech Republic (43), in Germany (44), and in Japanese men residing in Hawaii (45). A 2011 meta-analysis of prospective cohort and case-control studies found that moderate consumption of wine or beer was associated with a decreased risk of non-fatal vascular events (46). This analysis did not associate drinking liquor with cardiovascular benefit, although the authors noted that binge drinking — which is known to increase CHD risk — was apparent in several of the included studies (46).

Socioeconomic status and lifestyle characteristics (e.g., tobacco use, exercise habits) may differ among people who prefer wine, beer, or liquor, and this may in part explain any additional benefit of one beverage type observed in some studies. For example, several early studies found that people who prefer wine tend to have higher incomes, have more formal education, smoke less, and eat more fruit and vegetables and less saturated fat than people who prefer other alcoholic beverages (47-49). These potential confounders should be controlled or adjusted for in the analysis of observational data.

Thus, although moderate alcohol consumption has been consistently associated with 20%-30% reductions in CHD risk, it is not yet clear whether drinking a specific type of alcoholic beverage might confer additional cardiovascular benefit.

Stroke

Ischemic strokes, which represent 87% of all strokes, are the result of insufficient blood flow to an area of the brain, which may occur when an artery supplying the brain becomes blocked by a blood clot (50). Hemorrhagic strokes occur when a blood vessel ruptures and bleeds into the brain. Although they are less prevalent than ischemic strokes, hemorrhagic strokes are generally more severe and contribute disproportionately to overall stroke mortality (51). Light or moderate alcohol consumption has been associated with a reduced risk of ischemic stroke, but not hemorrhagic stroke, in a number of observational studies (52-58). When the results of 19 prospective cohort and 16 case-control studies of alcohol consumption and the risk of stroke were combined in a meta-analysis, moderate alcohol consumption was associated with a significant reduction in the risk of ischemic stroke (59). Overall, those who consumed one or two drinks daily had a 28% lower risk of ischemic stroke than those who did not consume alcohol. Another meta-analysis of more recent studies (1980-2009) confirmed that moderate alcohol consumption was protective against only ischemic stroke in both men and women (60). A more recent meta-analysis of 27 prospective cohort studies found that light-to-moderate alcohol consumption (<15 grams/day) in women was associated with a reduced risk of ischemic (RR, 0.72) but not hemorrhagic stroke; moderate alcohol consumption (15-30 grams/day) was not linked to either type of stroke in men in this analysis (61).

Thus, light-to-moderate alcohol consumption appears to decrease risk of ischemic stroke, but not hemorrhagic stroke, likely due to the anti-thrombotic effect of alcohol.

Peripheral arterial disease

Just as atherosclerosis of the arteries supplying the heart muscle leads to coronary heart disease, atherosclerosis of the arteries of the extremities leads to peripheral arterial disease (PAD). When atherosclerosis is severe enough to diminish blood flow to the legs, even walking may result in leg or hip pain known as intermittent claudication (62). Impaired vascular endothelial function is also characteristic of the disease and may contribute to the clinical symptoms (63).

Although much less consistent than the evidence for heart disease and stroke, there is limited evidence that moderate alcohol consumption is associated with decreased risk of PAD. Four prospective cohort studies have found moderate alcohol consumption to be associated with significant decreases in several different indicators of PAD (64-67). One of these studies found that the inverse association between alcohol intake and PAD risk was significant in nonsmokers but not smokers, suggesting that the adverse effects of cigarette smoking on PAD risk may outweigh any protective effects of alcohol consumption (64).

Heart failure

Coronary heart disease is a major cause of heart failure. A prospective study in a cohort of 21,601 men and another in a cohort of 126,236 men and women found that moderate alcohol intake was inversely associated with heart failure, especially heart disease related to CHD (68, 69). More recently, in a cohort of 4,490 older adults (65 years or older at baseline) followed for more than 20 years (1,380 cases of heart failure), drinking one or more alcoholic drink per week was associated with a 26% lower risk of heart failure compared to abstainers (70).

Sudden cardiac death

While several studies have found that heavy alcohol consumption increases risk of sudden cardiac death (SCD; see below), the association of light-to-moderate alcohol consumption and SCD is less clear. Studies on this association have reported mixed results, but the two largest prospective cohort studies to date have found a lower risk of SCD with light-to-moderate alcohol consumption (71, 72).

Type 2 diabetes mellitus

Three meta-analyses have found a U-shaped relationship between alcohol consumption and incidence of type 2 diabetes mellitus, with greater protection being observed for women (73-75). The most recent meta-analysis included 20 prospective cohort studies and associated moderate alcohol consumption (22-25 grams of alcohol daily or 1.6-1.8 drinks/day) with a 40% risk reduction for women and a 13% risk reduction for men compared to lifetime alcohol abstainers (74). Heavy alcohol consumption (62 grams/day or 4.4. drinks/day for men and 51 grams/day or 3.6 drinks/day for women) was associated with an increased risk for type 2 diabetes (74).

Increased insulin secretion by the pancreas and decreased insulin sensitivity are important factors leading to the development of type 2 diabetes. Research suggests that moderate alcohol intake may decrease serum insulin levels, increase adiponectin (an adipocyte hormone inversely associated with type 2 diabetes) levels (25), and improve insulin sensitivity (76-79). On the other hand, heavy alcohol consumption may increase the risk of type 2 diabetes by contributing to obesity, especially abdominal obesity, disturbing carbohydrate metabolism, and/or impairing pancreatic or liver function (80).

Osteoporosis

Osteoporosis, a condition common among the elderly, results from progressive loss of bone mineral density (BMD). Several observational studies have associated light or moderate alcohol consumption with higher BMD in older adults compared to abstainers (81-91). Some studies have found stronger protective relationships among wine (89) or beer drinkers (89, 90) in comparison to those who consume liquor, suggesting that non-alcohol components (e.g., silicon in beer) might help explain the association. The effects of alcohol on bone health may also be dependent on age, gender, and hormonal status (reviewed in 92).

It is important to note that the available data come from observational studies, and the observed associations may be confounded, e.g., individuals who consume alcohol in moderation may have an overall healthier lifestyle than those who drink heavily or abstain. However, a recent study in perimenopausal women found that moderate alcohol intake was associated with improved BMD independent of various lifestyle factors, including smoking status, fruit and vegetable intake, and physical activity level (90).

Cognitive decline, dementia, and Alzheimer's disease

Although alcoholism and heavy alcohol consumption (>3-4 drinks/day) is known to increase the risk of cognitive impairment and dementia (93-95), recent meta-analyses and reviews have reported that light-to-moderate alcohol consumption in older adults is associated with a decreased risk of dementia and Alzheimer's disease when compared to abstention (93, 96, 97). Some meta-analyses have not found a significant reduced risk for vascular type dementia (96, 98) or for cognitive decline (93, 96, 98, 99). A few studies have suggested that consumption of wine may be especially protective against dementia, although inconsistent findings have been observed, and many studies have not distinguished among the various types of alcohol.

At least three epidemiological studies have used magnetic resonance imaging (MRI) to examine relationships between alcohol intake and subclinical abnormalities in the brains of healthy middle-aged or older adults. Two studies found that infarctions (areas of dead tissue) were less frequent in the brains of those reporting light or moderate alcohol intake compared to those who abstained from alcohol (100, 101). However, another study found no relationship between alcohol intake and the presence of infarction (102). Two of the studies measuring brain atrophy, a characteristic of Alzheimer's disease and alcoholic dementia, found brain atrophy to be lower in those who abstained from alcohol compared to alcohol consumers (100, 102). The other study found less brain atrophy with light-to-moderate alcohol consumption but only in carriers of the apolipoprotein E (APOE) ε4 allele, who are at increased risk for Alzheimer's disease (101). Because of the complex nature of alcohol's effects on the brain, further research is needed to determine the risks and benefits of alcohol consumption with respect to cognitive function and dementia.

Gallstones

The majority of prospective cohort studies (103-107) and case-control studies (108, 109) have found that men and women with moderate alcohol intakes have lower risks of gallstones or gallbladder surgery (cholecystectomy) than those who do not consume alcohol. Although the reasons for the consistent inverse association between moderate alcohol consumption and gallstone incidence are not entirely clear, regular alcohol intake may result in bile that is less likely to crystallize into gallstones or stimulate gallbladder emptying (106).

Health Risks of Moderate Alcohol Consumption

Pregnancy

Fetal alcohol spectrum disorders (FASD) is a continuum of developmental abnormalities resulting from gestational alcohol exposure; FASD may affect as many as 1%-2% of US children (110, 111). Fetal alcohol syndrome (FAS) — a severe FASD — is a cluster of physical and mental birth defects associated with heavy alcohol consumption during pregnancy. Some characteristics of FAS include facial abnormalities, mental retardation, and growth impairment. More moderate alcohol consumption during pregnancy (7-14 drinks/week) has been associated with more subtle effects on cognitive and behavioral development (112, 113). Children of mothers who drank moderately during pregnancy have been found to have problems with memory, attention and learning, and behavior (114). Overall, studies on the association of low-to-moderate drinking during pregnancy and mental health of offspring have reported mixed results (reviewed in 115). However, it is important to note that these studies are observational in nature and may have not adequately controlled for potential confounding factors (e.g., lifestyle differences [in women who drank alcohol during pregnancy versus those who abstained] that influence mental development) (115).

Since no safe level of alcohol consumption has been established at any stage of pregnancy, pregnant women and women who are planning a pregnancy should abstain from alcohol (116, 117).

Breast cancer

More than 100 observational studies have been completed on the association between alcohol consumption and female breast cancer, with most finding an increased risk (118-121). Even though the available data come from observational studies, many consider the association to be causal. Regular alcohol consumption as low as one or two drinks per day has been associated with modest but significant increases in breast cancer risk. A threshold for harm, however, is difficult to define due to potential underreporting of alcohol intake by heavy drinkers, which could result in heavy drinkers being misclassified as 'moderate alcohol consumers' (122).

A linear dose-dependent relationship between alcohol consumption and breast cancer risk has been observed for premenopausal and postmenopausal breast cancer regardless of the type of alcoholic beverage consumed. Pooled and meta-analyses have found that each 10-gram increase in daily alcohol consumption (slightly less than one drink) is associated with a 7%-10% increased risk of breast cancer in women (123-125). Studies of alcohol consumption and breast cancer-specific mortality have reported mixed results, with a recent meta-analysis of 25 prospective cohort studies finding an increased risk only with alcohol consumption in excess of 20 grams (1.4 drinks)/day (126). Moderate alcohol consumption has been consistently associated with reduced risk of all-cause mortality (see Mortality above).

Although the mechanisms for the consistent association between alcohol intake and breast cancer incidence have not been clearly identified, proposed mechanisms include acetaldehyde formation, induction of CYP2E1 metabolism and increased oxidative stress, increased circulating estrogen or androgen levels, and enhanced invasiveness of breast cancer cells (119, 127). Current estimates are that about one in eight women (12.4%) in the US will develop breast cancer at some point in her lifetime (128). Although there are many risk factors for breast cancer, alcohol consumption is one of only a few modifiable risk factors.

Folate and breast cancer

Alcohol interferes with the absorption, transport, and metabolism of folate, which is required for DNA methylation and DNA repair (see the article on Folate). Alterations in these processes may result in mutations or altered gene expression, which increase the risk of cancer (118). Several (129-134), but not all (135-139), studies have found that sufficient folate intake may modify the association between alcohol intake and breast cancer risk. Although the interactions between folate, alcohol, and breast cancer risk remain to be clarified, it makes sense for women who drink alcohol to take a daily multivitamin containing 400 μg of folic acid.

Progression to heavy or hazardous drinking

Some people, such as recovering alcoholics and those with family histories of alcohol abuse or alcoholism, may not be able to maintain moderate drinking habits. Susceptibility to alcoholism is affected by genetic, psychosocial, and environmental factors. Children of an alcoholic parent have been found to be at significantly higher risk of developing alcoholism than those without an alcoholic parent (140). This increase in risk is likely related to interactions between genetic factors and factors related to the family environment. The National Institute on Alcohol Abuse and Alcoholism recommends that people with a family history of alcoholism, especially in a parent, approach moderate drinking carefully (141).

Medication interactions

In the liver, alcohol is metabolized by the same enzymes as many medications. Therefore, alcohol consumption can affect the activation or breakdown of a number of medications. The consumption of alcohol may also increase sedation, drowsiness, and hypotensive effects caused by numerous prescription and over-the-counter medications. Although serious interactions between alcohol and medications are more common in the presence of heavy alcohol consumption, even moderate alcohol consumption may hypothetically increase the risk of some adverse reactions in susceptible people (142). Women and older adults are particularly at risk for interactions between alcohol and medications (143, 144).

Many different classes of prescription medication may interact adversely with alcohol, including antibiotics, anticonvulsants, anticoagulants (e.g., Coumadin), antidepressants, antidiabetic agents, antihypertensive agents, vasodilators (e.g., nitrates and calcium channel blockers), barbiturates, benzodiazepines (sedatives), histamine H_2-receptor blockers, muscle relaxants, and narcotic and non-narcotic pain relievers. Over-the-counter medications and herbal preparations may also interact with alcohol, including pain medications like aspirin, acetaminophen (Tylenol), ibuprofen (Advil, Motrin), and naproxen sodium (Aleve); cold and allergy medications like diphenhydramine (Benadryl) and chlorpheniramine; heartburn medications like cimetidine (Tagamet) and ranitidine (Zantac); and herbal preparations like chamomile, valerian, and kava.

To help avoid potentially serious interactions between alcohol and medications, make sure your health care provider is aware of your alcohol intake. Before taking prescription or over-the-counter medications, read the product warning labels or consult a pharmacist or health care provider to determine whether alcohol consumption increases the risk of adverse effects. It may, in general, be advisable to separate taking any medication and drinking alcohol by two to three hours. For more information on potentially serious interactions between alcohol and medications, see the National Institute on Alcohol Abuse and Alcoholism website.

Health Benefits of Heavy Alcohol Consumption

None

Health Risks of Heavy Alcohol Consumption

Pregnancy

Heavy consumption of alcohol during pregnancy causes fetal alcohol syndrome (FAS). See above.

Cardiovascular disease

Hypertension

Heavy alcohol consumption has been consistently associated with an increased risk of high blood pressure (hypertension) in prospective cohort and case-control studies (145-147). A 2009 systematic review and meta-analysis of 12 prospective cohort studies found consuming 50 grams (3.6 drinks)/day of alcohol was associated with a 1.6-fold and 1.8-fold higher risk of hypertension in men and women, respectively; alcohol intake at twice that level (100 grams (~7 drinks)/day) was associated with a relative risk of 2.5 for men and 2.8 for women (148).

The results of numerous clinical trials indicate that reducing alcohol intake lowers blood pressure in hypertensive and normotensive individuals. A meta-analysis that combined the results of 15 randomized controlled trials found that reducing alcohol consumption resulted in significant decreases in both systolic and diastolic blood pressure (149).

Stroke

Ischemic strokes are the result of insufficient blood flow to an area of the brain, which may occur when an artery supplying the brain becomes blocked by a blood clot. Hemorrhagic strokes occur when a blood vessel ruptures and bleeds into the brain. Although regular, moderate alcohol consumption has been associated with decreased risk of ischemic stroke in some studies, heavy alcohol consumption has been associated with increased risk of both ischemic stroke and hemorrhagic stroke. A meta-analysis that combined the results of 19 prospective cohort and 16 case-control studies found that heavy drinking more than doubled the risk of hemorrhagic stroke and increased the risk of ischemic stroke by 70% (59). A meta-analysis of recent studies (1980-2009) confirmed that heavy drinking is associated with increased risks of ischemic and hemorrhagic stroke in both men and women (60). Heavy alcohol consumption may increase the risk of stroke by contributing to hypertension, cardiomyopathy (heart muscle damage), cardiac rhythm disturbances, and coagulation (clotting) disorders and impaired hemostasis.

Cardiac arrhythmias and sudden cardiac death

The long-recognized association between bouts of heavy alcohol consumption and cardiac rhythm disturbances (arrhythmias) was called "holiday heart syndrome" because it was first described in people who were admitted to hospitals after holidays or weekends (150). Atrial fibrillation is the cardiac arrhythmia most commonly associated with heavy alcohol use (151, 152). A 2010 systematic review and meta-analysis found a dose-dependent association between daily alcohol consumption and risk of this type of cardiac arrhythmia, with an increased risk being found with consumption greater than 24 grams/day (1.7 drinks/day) for women and 36 grams/day (2.6 drinks/day) for men (153). A 2014 meta-analysis of seven prospective studies found that consumption of more than two drinks per day was associated with increased risk of atrial fibrillation in men and women, and the risk increased by 8% with each additional daily drink (154, 155). Additionally, several studies have found that heavy alcohol consumption (>5 drinks per day) increases risk of sudden cardiac death (SCD) (156, 157).

The ways by which alcohol may trigger arrhythmias and SCD are not fully known. Alcohol may interfere with the contractility of heart muscle cells, change the shape and structure of heart muscle cells, contribute to electrolyte imbalance, and/or induce oxidative stress (158).

Alcoholic cardiomyopathy

Alcoholic cardiomyopathy is a heart muscle disease caused by long-term, heavy alcohol consumption (159); this disease likely occurs in only a small proportion (<10%) of heavy drinkers (160). Alcoholic cardiomyopathy occurs in two stages: (1) an early asymptomatic stage, when the damage to the heart muscle has no obvious symptoms; and (2) a symptomatic stage, when the heart muscle is too weak to pump effectively. Although the level of alcohol consumption resulting in alcoholic cardiomyopathy has not been clearly established, people consuming at least seven alcoholic drinks daily for more than five years are thought to be at risk of developing asymptomatic alcoholic cardiomyopathy. Those who continue to drink heavily ultimately develop heart failure. Research suggests that women may be more susceptible to alcohol's toxic effects on the heart muscle than men (161, 162).

Alcoholic liver disease

Chronic excessive alcohol use is a major cause of illness and death from liver disease (163). Alcoholic liver disease is characterized by a spectrum of liver injury, including steatosis (fatty liver), hepatitis (a potentially fatal inflammation of the liver), fibrosis, and cirrhosis — the most advanced form of alcoholic liver disease. In cirrhosis, the formation of fibrotic scar tissue results in progressive deterioration of liver function. Complications of advanced liver disease include severe bleeding from distended veins in the esophagus (esophageal varices), brain damage (hepatic encephalopathy), fluid accumulation in the abdomen (ascites), and kidney failure.

A 2004 meta-analysis of nine studies found a dose-responsive increase in risk for liver cirrhosis with increasing amounts of alcohol consumed: relative risks (RR) of 2.9 for 25 grams (1.8 drinks)/day, 7.1 for 50 grams (3.6 drinks)/day, 26.5 for 100 grams (7.1 drinks)/day (164). Another meta-analysis found a higher RR for liver cirrhosis with increasing doses but also suggested a threshold response for morbidity from liver cirrhosis (higher risk in women with consumption >24 g (1.7 drinks)/day of alcohol, and higher risk in men with consumption >36 g (2.6 drinks)/day of alcohol) (165). Risk of mortality from liver cirrhosis was increased with any alcohol consumption in women and with consumption of >12 g (0.9 drinks)/day in men; a stronger relationship between alcohol consumption and mortality from liver cirrhosis versus morbidity might be expected because alcohol consumption is known to exacerbate any existing liver disease (165).

Serious liver disease has been found to develop in approximately 10% of those who consume more than 60 grams per day of alcohol (4.3 drinks/day). Women are more susceptible to serious alcoholic liver disease than men (165, 166), and individuals with hepatitis C infection have an increased risk of alcoholic liver disease (167).

Cancer

Heavy alcohol consumption has been found to increase the risk of cancer at a number of sites (168). Heavy alcohol consumption is consistently and dose-dependently associated with increases in risk of cancers of the mouth, pharynx, larynx, esophagus, liver, colon, rectum, and breast (165). Moreover, the combination of smoking and alcohol results in even more dramatic increases in cancer risks (169). Increased risk of liver cancer with long-term heavy alcohol consumption may be related to alcoholic cirrhosis of the liver or increased susceptibility to cancer caused by viral hepatitis.

Alcohol-related brain disorders

Chronic heavy alcohol use and alcohol dependence are associated with detrimental effects on the brain and its function, especially memory and executive functions (170). Alcoholics have been observed to suffer from cerebral atrophy (shrinkage of brain tissue), which likely contributes to alcohol-associated dementia and cognitive impairment (94). In contrast to the progressive cerebral atrophy observed in Alzheimer's disease, alcohol-related cerebral atrophy may decrease after a period of abstinence. Alcohol-related brain disorders may be associated with nutritional deficiencies like thiamin (171) or niacin (172).

Pancreatitis

Pancreatitis is a painful inflammation of the pancreas. Acute pancreatitis is characterized by the sudden onset of severe upper abdominal pain, often accompanied by nausea and vomiting (173). Although most attacks of acute pancreatitis require only supportive care, a small percentage of people may experience serious or life-threatening complications. Studies estimate that 19%-32% of acute pancreatitis cases have an alcoholic etiology (reviewed in 174).

Chronic pancreatitis results in progressive destruction of the pancreas, leading to loss of pancreatic function (175). An estimated 60%-72% of chronic pancreatitis cases have an alcoholic etiology. The risk of developing chronic pancreatitis increases with the quantity and duration of alcohol consumed: an increased risk of chronic pancreatitis is observed with long-term consumption of five or more alcoholic drinks per day (174). Only a small percentage (<10%) of alcoholics develop clinical pancreatitis; thus, hereditary and environmental factors are also thought to play a role. The disease is more common in men than in women, in Blacks compared to Whites, and in smokers versus nonsmokers (176, 177).

Bone health

Chronic alcoholism has deleterious effects on bone health, including decreased bone mineral density and increased risk of fracture. Consumption of large quantities of alcohol (100-200 grams/day) directly impairs activity of osteoblasts — the bone-forming cells. Negative effects on bone health are also indirectly caused by the malnutrition experienced by alcoholics (92).

Accidents, injury, and violence

Alcohol use is associated with an increased risk of injury in a number of circumstances, including motor vehicle accidents, falls, and fires (178). Data from hospital emergency departments indicate that consuming as little as one or two alcoholic drinks in the previous six hours significantly increases the risk of injury (179). Thirty-one percent of all traffic fatalities in the US are alcohol-related (180). Although the legal blood alcohol concentration (BAC) limit for drivers is 0.08 (grams of alcohol/deciliter of blood) in the US, most scientific studies have found significant impairment of driving-related skills at a BAC of 0.05 (181). For reference, a BAC of 0.05 might be achieved by a 175-pound male consuming three standard alcoholic drinks in one hour or a 120-pound female consuming two drinks in one hour (182).

Excessive alcohol use is associated with all forms of violence, including suicide, homicide, domestic violence, sexual assault, and gang violence. Although the reasons for alcohol-associated violence are complex, alcohol use appears to increase the risk of violent behavior in some populations (183).

Mortality

Heavy alcohol consumption increases the risk of mortality (4, 16). As mentioned above, the relationship between alcohol consumption and mortality is often described as J-shaped, meaning those with high intakes of alcohol have a higher risk of mortality than nondrinkers. A 2011 meta-analysis of eight prospective cohort studies found that consumption of >60 grams/day of alcohol was associated with a 30% increase in mortality from all causes (16).

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Micronutrients and Health

Select a topic from the list for more information.

- Bone Health
- Cognitive Function
- Immunity
- Inflammation
- Skin Health
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  - Vitamin C
  - Vitamin D
  - Vitamin E
  - Minerals
  - Essential Fatty Acids
  - Flavonoids
  - Peptides

Life Stages

Nutritional needs change throughout the life cycle. Growth and development during infancy, childhood, and adolescence require special intakes of many micronutrients. Nutritional needs also change throughout the stages of adulthood. For example, micronutrient requirements during pregnancy and lactation are increased, and micronutrient needs of older adults reflect age-related changes in nutrient absorption and metabolism.

This section of the site is under development; new articles will be added in the future.

- Children Ages 4 to 13 Years
- Adolescents
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- Older Adults

Children

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Micronutrient Requirements of Children Ages 4 to 13 Years

Introduction

The period of childhood between ages 4 and 13 years is characterized by continued physical growth and rapid cognitive, emotional, and social development (1, 2). Many children, especially girls, undergo their pubertal growth spurt between ages 4 and 13. This period of childhood precedes adolescence — the transitional stage of development between childhood and adulthood. Due to increased growth and metabolism, the nutritional requirements of children are higher in proportion to body weight compared with adults (1, 3). Good nutrition throughout childhood is important not only to support normal growth and cognitive development but also to establish healthy eating patterns that are associated with decreased risk of chronic conditions and diseases in adulthood, including obesity, type 2 diabetes, cardiovascular disease, metabolic syndrome, and osteoporosis.

Inadequate intake of nutrients can impair growth and development in children. This article discusses micronutrient (vitamins and nutritionally essential minerals) requirements of children ages 4 to 13 years. The Food and Nutrition Board (FNB) of the Institute of Medicine establishes dietary reference intakes (DRIs) for each micronutrient; these reference values should be used to plan and assess dietary intakes in healthy people (4, 5). The DRIs include the estimated average requirement (EAR), the recommended dietary allowance (RDA), the adequate intake (AI), and the tolerable upper intake level (UL). The RDA, which is the average daily dietary intake level of a nutrient sufficient to meet the requirements of almost all (97.5%) healthy individuals in a specific life stage and gender group, should be used in the planning of diets for individuals (6). An AI recommendation is set when an RDA cannot be determined. In children, these intake recommendations are based on data regarding average micronutrient intakes of children and also on certain criteria for micronutrient adequacy. However, because of limited data, many of the micronutrient intake recommendations for children are extrapolated from recommendations for adults using a formula that accounts for metabolic body weight and growth (3). Metabolic body weight is determined by calculating the 0.75 power of body mass (body mass^0.75) (7). To account for growth, the equation used to derive an RDA or AI involves an age group-specific growth factor (3). The FNB establishes separate dietary intake recommendations for children between the ages of 4 to 8 years and those between the ages of 9 and 13 years (see Ages 4 to 8 Years and Ages 9 to 13 Years).

Micronutrient Needs of Children Ages 4 to 8 Years

For each micronutrient, the FNB sets an RDA or AI for children ages 4 to 8 years; these micronutrient intake recommendations do not differ with gender for this age group. **Table 1** lists the RDA for each micronutrient. As mentioned above, the RDA should be used in the planning of diets for individuals. A few select micronutrient requirements for children are discussed below.

Table 1. Dietary Reference Intakes Set by the FNB:
RDA for Micronutrients During Childhood, Ages 4 to 8 Years

Micronutrient	Males and Females
Biotin	12 μg/day (AI)
Folate	200 μg/day^a
Niacin	8 mg/day^b
Pantothenic Acid	3 mg/day (AI)
Riboflavin	600 μg/day
Thiamin	600 μg/day
Vitamin A	400 μg/day (1,333 IU/day)^c
Vitamin B$_6$	600 μg/day
Vitamin B$_{12}$	1.2 μg/day
Vitamin C	25 mg/day
Vitamin D	15 μg/day (600 IU/day)
Vitamin E	7 mg/day (10.5 IU/day)^d
Vitamin K	55 μg/day (AI)
Calcium	1,000 mg/day
Chromium	15 μg/day (AI)
Copper	440 μg/day
Fluoride	1 mg/day (AI)
Iodine	90 μg/day
Iron	10 mg/day
Magnesium	130 mg/day
Manganese	1.5 mg/day (AI)
Molybdenum	22 μg/day
Phosphorus	500 mg/day
Potassium	2,300 mg/day (AI)
Selenium	30 μg/day
Sodium	1,000 mg/day (AI)
Zinc	5 mg/day
Choline^e	250 mg/day (AI)
α-Linolenic Acid^e	900 mg/day (AI)
Linoleic Acid^e	10 g/day (AI)

AI, adequate intake
^{a}Dietary Folate Equivalents
^{b}NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin
^{c}Retinol Activity Equivalents
^{d}α-Tocopherol
^{e}Considered an essential nutrient, although not strictly a micronutrient

Micronutrient Needs of Children Ages 9 to 13 Years

For each micronutrient, the FNB sets an RDA or AI for children ages 9 to 13 years; these recommendations are gender specific to account for the unique nutritional needs of boys and girls as they undergo puberty. **Table 2** lists the RDA for each micronutrient by gender. The RDA should be used in the planning of diets for individuals. A more detailed discussion of the requirements of certain micronutrients for children can be found below.

Table 2. Dietary Reference Intakes Set by the FNB:
RDA for Micronutrients During Childhood, Ages 9 to 13 Years

Micronutrient	Males	Females
Biotin	20 μg/day (AI)	20 μg/day (AI)
Folate	300 μg/day^a	300 μg/day^a
Niacin	12 mg/day^b	12 mg/day^b
Pantothenic Acid	4 mg/day (AI)	4 mg/day (AI)
Riboflavin	900 μg/day	900 μg/day
Thiamin	900 μg/day	900 μg/day
Vitamin A	600 μg/day (2,000 IU/day)^c	600 μg/day (2,000 IU/day)^c
Vitamin B$_6$	1 mg/day	1 mg/day
Vitamin B$_{12}$	1.8 μg/day	1.8 μg/day
Vitamin C	45 mg/day	45 mg/day
Vitamin D	15 μg/day (600 IU/day)	15 μg/day (600 IU/day)
Vitamin E	11 mg/day (16.5 IU/day)^d	11 mg/day (16.5 IU/day)^d
Vitamin K	60 μg/day (AI)	60 μg/day (AI)
Calcium	1,300 mg/day	1,300 mg/day
Chromium	25 μg/day (AI)	21 μg/day (AI)
Copper	700 μg/day	700 μg/day
Fluoride	2 mg/day (AI)	2 mg/day (AI)
Iodine	120 μg/day	120 μg/day
Iron	8 mg/day	8 mg/day
Magnesium	240 mg/day	240 mg/day
Manganese	1.9 mg/day (AI)	1.6 mg/day (AI)
Molybdenum	34 μg/day	34 μg/day
Phosphorus	1,250 mg/day	1,250 mg/day
Potassium	2,500 mg/day (AI)	2,300 mg/day (AI)
Selenium	40 μg/day	40 μg/day
Sodium	1,200 mg/day (AI)	1,200 mg/day (AI)
Zinc	8 mg/day	8 mg/day
Choline^e	375 mg/day (AI)	375 mg/day (AI)
α-Linolenic Acid^e	1,200 mg/day (AI)	1,000 mg/day (AI)
Linoleic Acid^e	12 g/day (AI)	10 g/day (AI)

AI, adequate intake
^{a}Dietary Folate Equivalents
^{b}NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin
^{c}Retinol Activity Equivalents
^{d}α-Tocopherol
^{e}Considered an essential nutrient, although not strictly a micronutrient

Vitamins

Vitamin A

Vitamin A is a fat-soluble vitamin that is essential for growth and development, normal vision, the expression of selected genes, and immunity (see the article on Vitamin A). Vitamin A deficiency is a major public health problem worldwide. It is the leading preventable cause of blindness among children in developing nations (8). The earliest evidence of vitamin A deficiency is impaired dark adaptation or night blindness. Mild vitamin A deficiency may result in Bitot's spots, which are changes in the conjunctiva (the mucous membrane that lines the eyelids and the outer surface of the eye). Severe or prolonged vitamin A deficiency causes a condition called xerophthalmia (dry eye), characterized by changes in the cells of the cornea (clear covering of the eye) that ultimately result in corneal ulcers, scarring, and blindness (9, 10).

Vitamin A deficiency also places children at a heightened risk for infectious disease; in fact, vitamin A deficiency can be considered a nutritionally acquired immunodeficiency disorder (11). Even children who are only mildly deficient in vitamin A have a higher incidence of respiratory disease and diarrhea, as well as a higher rate of mortality from infectious disease, compared to children who consume sufficient vitamin A (12). Vitamin A supplementation in children has been found to decrease both the severity and incidence of deaths related to diarrhea and measles in developing countries, where vitamin A deficiency is common (13). The onset of infection reduces blood retinol (preformed vitamin A) levels very rapidly. This phenomenon is generally believed to be related to decreased synthesis of retinol binding protein (RBP) by the liver. In this manner, infection stimulates a vicious cycle, because inadequate vitamin A nutritional status is related to increased severity and likelihood of death from infectious disease (14).

The RDA for vitamin A is based on the amount needed to ensure adequate stores (four months) of vitamin A in the body to support normal reproductive function, immune function, vitamin A-dependent gene expression, and vision (15). Vitamin A intake recommendations for children were derived by extrapolating the recommendation for adults using metabolic body weight, accounting for growth. The RDA for children ages 4 to 8 years is 400 μg/day of Retinol Activity Equivalents (RAE), which is 1,333 international units (IU); the RDA for both boys and girls ages 9 to 13 years is 600 μg/day of RAE, which is equivalent to 2,000 IU. For information on vitamin A content in foods, see the article on Vitamin A.

Vitamin B$_{12}$

Vitamin B$_{12}$ is needed for two sorts of reactions in the human body. One is transmethylation (methyl transfer between two molecules) that leads to the synthesis of the amino acid methionine from homocysteine. Methionine, in turn, is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, such as the methylation of sites within DNA and RNA (16). The second sort of reaction is isomerization (rearrangement of a molecule). Vitamin B$_{12}$ acts as a coenzyme for methylmalonyl-CoA mutase to convert methylmalonyl-CoA to succinyl-CoA, an important step for the metabolism of proteins and lipids. Both transmethylation and isomerization reactions are essential for the metabolism of components of the myelin sheath of nerve cells and for the metabolism of neurotransmitters. Accordingly, vitamin B$_{12}$ deficiency damages the myelin sheath covering cranial, spinal, and peripheral nerves, resulting in neurological damage (17, 18). The myelin sheath is the insulating layer of tissue made up of lipids and proteins that surrounds nerve fibers. This sheath acts as a conduit in an electrical system, allowing rapid and efficient transmission of nerve impulses (19). In some cases, neurologic symptoms caused by vitamin B$_{12}$ deficiency can be reversed by vitamin treatment (18), but reversibility seems to be dependent upon the duration of the associated neurologic complications (20).

Although myelination primarily occurs during fetal development and early infancy, it continues through childhood, adolescence, and stages of early adulthood (21, 22). Because of the role of vitamin B$_{12}$ in myelination and other metabolic processes, it is important for children to meet dietary intake recommendations. The RDA of vitamin B$_{12}$ for children ages 4 to 8 years is 1.2 μg/day, and the RDA for boys and girls ages 9 to 13 years is 1.8 μg/day. This vitamin is naturally present only in animal products, such as meat, poultry, fish (including shellfish), and to a lesser extent in milk, but it is not generally present in plant products or yeast (9). Thus, children who have vegan diets need supplemental vitamin B$_{12}$ or need adequate intake from fortified foods.

Vitamin C

Vitamin C has a number of important roles during growth and development, including being required for the synthesis of collagen, carnitine, and neurotransmitters (23). Vitamin C is also a highly effective antioxidant and is important for immunity (see the article on Immunity). Further, vitamin C strongly enhances the absorption of non heme iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) and forming an absorbable, iron-ascorbic acid complex. Specifically, iron absorption is 2- to 3-fold higher with co-ingestion of 25 to 75 mg of vitamin C (24). This has special relevance to child health, considering the fact that iron deficiency is the most common nutrient deficiency in the world (see Iron below). Vitamin C intake recommendations for children are extrapolated from recommendations for adults based on relative body weight. The RDA for children ages 4 to 8 years is 25 mg/day, and the RDA for boys and girls ages 9 to 13 years is 45 mg/day (25). For information on food sources, see the article on Vitamin C.

Vitamin D

Vitamin D is a fat-soluble vitamin that is essential for maintaining normal calcium metabolism and is thus necessary for bone health. Severe vitamin D deficiency in infants and children results in the failure of bone to mineralize, leading to a condition known as rickets. Rapidly growing bones are most severely affected by rickets. The growth plates of bones continue to enlarge, but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. In severe cases of vitamin D deficiency, low serum calcium levels (hypocalcemia) may induce seizures. Although fortification of foods has led to complacency regarding vitamin D deficiency, nutritional rickets is still being reported in the United States and other nations (26-33).

In the US, fortified foods are a major contributor to dietary vitamin D intake, especially in children, because only a few foods naturally contain vitamin D (see the article on Vitamin D). In the US, milk is voluntarily fortified with 400 IU (10 μg) of vitamin D per quart (946 mL) (34), and other foods may be fortified with varying concentrations of vitamin D. According to a recent report regarding the American food supply, nearly all milk, about 75% of ready-to-eat breakfast cereals, around 50% of milk substitutes, about 25% of yogurts, and 8-14% of juices, cheeses, and spreads are fortified with vitamin D (35). Although not required by the US FDA to be listed on the Nutrition Facts food label, some packaged foods, particularly cereals, include the amount of vitamin D in one serving as the percentage of the Daily Value (DV). The DV is 400 IU, but the RDA for children ages 4 to 8 years and for boys and girls ages 9 to 13 years is 600 IU/day. In Canada, vitamin D fortification of milk and margarine is mandatory, with milk containing 35-45 IU per 100 mL (331-426 IU per quart) and margarine containing 530 IU per 100 grams (34), but vitamin D fortification of foods is less common in European nations (36). In addition to diet, vitamin D can be endogenously synthesized in the skin upon exposure to ultraviolet-B radiation from sunlight; however, sunscreens effectively block synthesis of vitamin D in skin (see the article on Vitamin D).

When setting the RDA for vitamin D, the FNB assumed minimal sun exposure, even though sun exposure could provide most people with their entire vitamin D requirement. For US children to meet the RDA of 600 IU/day (15 μg/day), about 6 cups of milk would need to be consumed each day. Analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2005-2006 found that average total vitamin D intakes (from diet and supplements combined) in US children of ages 4 to 8 were 9.3 μg/day (372 IU/day) for boys and 7.9 μg/day (316 IU/day) for girls (37). Even though the analysis found that 43% of boys and 34% of girls in this age group took supplements containing vitamin D (37), their average total daily intakes were well below the current RDA of 600 IU/day (15 μg/day). Total daily vitamin D intakes were even lower for chilren aged 9 to 13 years (boys, 7.5 μg or 300 IU/day; girls, 7.7 μg or 308 IU/day). Sun exposure can substantially affect body vitamin D levels, and measuring 25-hydroxyvitamin D — the major circulating form of vitamin D — is a useful indicator of vitamin D status. It is assumed that a dietary intake of 600 IU/day results in a serum 25-hydroxyvitamin D level of 50 nmol/L (20 ng/mL), which the FNB considers as the cut-point for vitamin D adequacy (38). However, higher serum 25-hydroxyvitamin D serum levels may benefit health; thus, the Linus Pauling Institute recommends that children ages 4 to 13 years should have a daily intake of 600 to 1,000 IU (15 to 25 μg) of vitamin D, consistent with the recommendations of the Endocrine Society (39). Given the average vitamin D content of the diets of children, supplementation may be necessary to meet these recommendations. The American Academy of Pediatrics currently suggests that all children receive 400 IU of supplemental vitamin D daily (26) — an amount that is typically found in multivitamin supplements.

The tolerable upper intake level (UL) — the highest level of daily intake of a specific nutrient likely to pose no risk of adverse health effects in almost all individuals — for children ages 4 to 8 years is 3,000 IU/day (75 μg/day) of vitamin D; the UL for boys and girls ages 9 to 13 years is 4,000 IU (100 μg/day).

Vitamin E

The RDA for vitamin E in children, expressed as an amount of the α-tocopherol form of the vitamin, was based on extrapolations from intake recommendations for adults, accounting for differences in lean body mass and increased needs of growth during childhood. The RDA is 7 mg/day (10.5 IU/day) for children ages 4 to 8 years and 11 mg/day (16.5 IU/day) for boys and girls ages 9 to 13 years (40). A US national survey, NHANES 1999-2000, found that children ages 4 to 8 years had an average intake of 5.2 mg/day of α-tocopherol; this survey found that average α-tocopherol intakes for boys and girls ages 9 to 13 years were 6.0 mg/day and 5.3 mg/day, respectively (41). These intakes are below the current RDA. Surveys in The Republic of Korea and Germany have also reported low intakes of vitamin E in children (42, 43). However, true vitamin E deficiency is rare and has been observed only in cases of severe malnutrition, genetic defects affecting the α-tocopherol protein, and fat malabsorption syndromes; see the article on Vitamin E.

Minerals

Calcium

About 99% of calcium in the body is found in bones and teeth (44). Adequate intake of calcium throughout childhood and adolescence is important for proper mineralization of growing bones, attainment of peak bone mass, and reduction of risk for osteoporosis in adulthood (38). Thus, dietary intake recommendations for calcium in children are established based on the calcium intake needed to support bone accretion and overall calcium retention (i.e., the dietary intake needed to achieve positive calcium balance) (38). The RDA is 1,000 mg/day for children ages 4 to 8 years and 1,300 mg/day for boys and girls ages 9 to 13 years. Calcium intake recommendations are higher in children ages 9 to 13 to account for increased needs of the mineral during puberty (38).

Many American children have dietary calcium intakes below current recommendations, with girls having lower intakes than boys. A recent study reported daily calcium intake in children using data from NHANES 2003-2006, a US national survey (37). An estimated 17% of boys and 33% of girls between the ages of 4 and 8 have total calcium intakes (dietary plus supplemental intakes) of 800 mg/day or less. For children in this age group, average intake from supplements in those who took supplemental calcium (29% of boys; 26% of girls) was 99 mg/day and 87 mg/day for boys and girls, respectively. In children 9 to 13 years old, only 23% of boys and 15% of girls met the RDA for calcium, even though 20% of boys and 24% of girls took supplemental calcium (average supplemental calcium intake of 104 mg/day for boys and 80 mg/day for girls) (37). Dairy products, which provide about 72% of the calcium in the American diet (44), represent rich and absorbable sources of calcium. Milk contains 300 mg of calcium per cup; therefore, children ages 4 to 8 and children ages 9 to 13 could meet the RDA for calcium by drinking 3.3 or 4.3 cups of milk daily, respectively. Certain vegetables and grains also provide calcium, but their bioavailability is lower compared with dairy. For more information on dietary sources of calcium and calcium bioavailability, see the article on Calcium. If children do not meet the RDA through diet alone, LPI recommends supplemental calcium. Children's multivitamin/mineral supplements generally provide no more than 150 mg of calcium.

The Nutrition Facts label of packaged foods lists calcium content in one serving as a percent of the Daily Value (DV), with the DV being 1,000 mg. Since the RDA for children ages 4 to 8 is 1,000 mg/day, the listed amount of calcium on the food label directly provides a percentage of the RDA. However, because the RDA for children ages 9 to 13 years is higher, the percentage of the DV listed would be an overestimation of the percentage of the RDA.

Fluoride

The mineral fluoride is important for the prevention of dental caries (tooth decay). Specific cariogenic (cavity-causing) bacteria found in dental plaque are capable of metabolizing certain carbohydrates (sugars) and converting them to organic acids that can dissolve tooth enamel. If unchecked, the bacteria may penetrate deeper layers of the tooth and progress into the soft pulp tissue at the center. Untreated caries can lead to severe pain, local infection, tooth loss or extraction, nutritional problems, and serious systemic infections in susceptible individuals (45). Increased fluoride exposure, most commonly through water fluoridation, has been found to decrease dental caries (46). Fluoride consumed in water appears to have a systemic effect in children before teeth erupt, as well as a topical (surface) effect in children and adults after teeth have erupted. The FNB set an adequate intake (AI) recommendation based on estimated intakes (0.5 mg/kg of body weight) that have been shown to reduce the occurrence of dental caries most effectively without causing the unwanted side effect of tooth enamel mottling, a white speckling or mottling of the permanent teeth known as dental fluorosis (47). The AI of fluoride for children ages 4 to 8 years is 1 mg/day, and the AI for boys and girls ages 9 to 13 years is 2 mg/day. For information about sources of fluoride, see the article on Fluoride.

Additionally, fluoridated toothpastes are very effective in preventing dental caries but add considerably to fluoride intake of children, especially young children who are more likely to swallow toothpaste. Researchers estimate that children under 6 years of age ingest an average of 0.3 mg of fluoride from toothpaste with each brushing, and swallowing fluoride-containing toothpaste is a major source of excess fluoride intake in this age group. Children who ingest more than two or three times the recommended fluoride intake are at increased risk of dental fluorosis. To prevent dental fluorosis while providing optimum protection from tooth decay, it is recommended that parents supervise children under 6 years of age while brushing with fluoridated toothpaste. In addition to discouraging the swallowing of toothpaste, children should be encouraged to use no more than a pea-size application of toothpaste and to rinse their mouths with water after brushing (47, 48). Fluoride supplements, available only by prescription, are intended for children living in areas with low water fluoride concentrations for the purpose of bringing their intake to approximately 1 mg/day (47). For more information about dental fluorosis, see the article on Fluoride.

Iodine

Iodine is required for the synthesis of the thyroid hormones, triiodothyronine (T$_3$) and thyroxine (T$_4$). To meet the body's demand for thyroid hormones, the thyroid gland traps iodine from the blood and incorporates it into thyroid hormones that are stored and released into the circulation when needed. In target tissues, such as the liver and the brain, T$_3$, the physiologically active thyroid hormone, can bind to thyroid receptors in the nuclei of cells and regulate gene expression. In target tissues, T$_4$, the most abundant circulating thyroid hormone, can be converted to T$_3$ by selenium-containing enzymes known as deiodinases. In this manner, thyroid hormones regulate a number of physiologic processes, including growth, development, metabolism, and reproductive function (49, 50).

Iodine deficiency is now accepted as the most common cause of preventable brain damage in the world. The spectrum of iodine deficiency disorders (IDD) includes mental retardation, hypothyroidism, goiter, and varying degrees of other growth and developmental abnormalities (49, 51). Iodine deficiency is associated with goiter; the incidence of goiter is higher in girls than boys. Children in iodine-deficient areas show poorer school performance, lower IQs, and a higher incidence of learning disabilities than matched groups from iodine-sufficient areas. A meta-analysis of 18 studies concluded that iodine deficiency alone lowered mean IQ scores in children by 13.5 points (52, 53).

Global estimates indicate that 31.5% of children between the ages of 6 and 12 years (266 million total children) has insufficient iodine intake (54). Major international efforts have produced dramatic improvements in the correction of iodine deficiency in the 1990s, mainly through the use of iodized salt in iodine-deficient countries (55). Today, 70% of households in the world use iodized salt (57), but iodine deficiency in children is still a major public health concern worldwide (57-59). For more information on the international effort to eradicate iodine deficiency, visit the websites of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) or the World Health Organization.

The RDA of iodine for children aged 4 to 8 years is 90 μg/day, and the RDA for boys and girls aged 9 to 13 years is 120 μg/day. The intake recommendation for children in this younger age group was based on results of a balance study in eight-year-old children who did not have goiters (60). Results of a balance study in children ages 9 to 13 years indicated that a minimum of 55 μg/day of iodine is needed (60), but the RDA for this older age group was set by extrapolating from the adult recommendation based on metabolic body weight (55). The amount of iodine in iodized salt and the contribution of iodized salt to total iodine intake vary by nation. In the US, iodized salt contains an average of 45 mg of iodine per kilogram and 20% of the salt consumed by Americans is iodized. Salt used in processed foods and the fast food industry is generally not iodized (61). However, the US is currently considered to be iodine-sufficient (62). Seafood is rich in iodine because marine animals can concentrate the iodine from seawater, and certain types of seaweed (e.g., wakame) are also very rich in iodine (see Table 3 in the article on Iodine). Dairy products are also relatively good sources of iodine. However, iodine content of plant foods depends on the iodine content of the soil (63).

Iron

Iron is an essential component of hundreds of proteins and enzymes involved in various aspects of metabolism, including oxygen transport and storage, electron transport and energy metabolism, antioxidant and beneficial pro-oxidant functions, oxygen sensing, and DNA synthesis (9, 64-68); see the article on Iron). Iron is stored in the body as ferritin, and serum level of ferritin is a good clinical indicator of iron status in children (69). Iron deficiency, which is the most common nutritional deficiency in the world, is a major public health problem, especially in developing nations, but it is also prevalent in industrialized nations. Severe iron deficiency leads to iron-deficiency anemia, which affects more than 30% of the global population (2 billion people) (70). Iron-deficiency anemia results when there is inadequate iron to support normal red blood cell formation. The anemia of iron deficiency is characterized as microcytic and hypochromic, meaning red blood cells are measurably smaller than normal and their hemoglobin content is decreased. At this most severe stage of iron deficiency, symptoms may be a result of inadequate oxygen delivery due to anemia and/or sub-optimal function of iron-dependent enzymes. Low red cell count, low hematocrit, and low hemoglobin concentrations are all used in the clinical diagnosis of iron-deficiency anemia (71). For details regarding the clinical diagnosis of iron-deficiency anemia, see Chapter 4 in the book, Nutritional Anemia, which is available through the Sight and Life website.

Most observational studies have found relationships between iron-deficiency anemia in children and poor cognitive development, poor school achievement, and behavior problems. However, it is difficult to separate the effects of iron-deficiency anemia from other types of deprivation in such studies, and confounding factors may contribute to the association between iron deficiency and cognitive deficits (72). Yet, several possible mechanisms link iron-deficiency anemia to altered cognition. For example, any cognitive benefit associated with iron supplementation could be possibly due to changes in nerve myelination, which have been observed in iron-deficient animals (73). Iron has an important role in the development of the cells that produce myelin (74); as noted above, the myelin sheath is the insulating layer of tissue comprised of lipids and proteins that surrounds nerve fibers. This sheath acts as a conduit in an electrical system, allowing for rapid and efficient transmission of nerve impulses (19). Iron is also important for enzymes involved in the synthesis of certain neurotransmitters and for DNA synthesis (75).

Children between the ages of 4 and 13 years are at lower risk of iron deficiency compared to younger or older children because infants, toddlers, and adolescents generally have higher growth rates (9). The RDA of iron for children ages 4 to 8 years is 10 mg/day, and the RDA for boys and girls ages 9 to 13 years is 8 mg/day. Girls in this latter age group who start to menstruate need an additional 2.5 mg/day of iron. These intake recommendations were based on a factorial modeling approach that accounts for the amount of iron needed to replace basal losses (losses in urine, feces, and sweat) and the iron requirements associated with growth (increases in hemoglobin, the oxygen-carrying pigment in red blood cells mass; increases in iron content of tissues; and for the younger age group, increases in iron storage). The intake recommendations also account for average bioavailability (the fraction of iron retained and used by the body) of dietary iron in these age groups (76).

The amount of bioavailable iron in food (or supplements) is influenced by the iron nutritional status of the individual and also by the form of iron (heme or nonheme). Individuals who are anemic or iron deficient absorb a larger percentage of the iron they consume (especially nonheme iron) than individuals who are not anemic and have sufficient iron stores (77, 78). In addition, heme iron, found in meat, poultry, and fish, is more readily absorbed and its absorption is less affected by other dietary factors than nonheme iron — the form found in plants, dairy products, fortified foods, and supplements. Although heme iron generally accounts for only 10-15% of the iron found in the diet, it may provide up to one third of total absorbed dietary iron (67, 77). The absorption of nonheme iron is strongly influenced by enhancers and inhibitors present in the same meal (77, 78). For instance, vitamin C strongly enhances the absorption of nonheme iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) and forming an absorbable, iron-ascorbic acid complex. Organic acids, such as citric, malic, tartaric, and lactic acids, also enhance nonheme iron absorption. Further, consumption of meat, poultry, and fish enhance nonheme iron absorption, but the mechanism for this increase in absorption is not clear (76, 77). Inhibitors of nonheme iron absorption include phytic acid, which is present in legumes, grains, and rice. In fact, small amounts of phytic acid (5 to 10 mg) can reduce nonheme iron absorption by 50%. The absorption of iron from legumes, such as soybeans, black beans, lentils, mung beans, and split peas, has been shown to be as low as 2% <a href=">(64, 76). Additionally, polyphenols found in some fruit, vegetables, coffee, tea, wines, and spices can markedly inhibit the absorption of nonheme iron, but this effect is reduced by the presence of vitamin C (64, 76). Soy protein, such as that found in tofu, has an inhibitory effect on iron absorption that is independent of its phytic acid content (76).

Magnesium

The mineral magnesium is involved in more than 300 essential metabolic reactions that are generally involved in energy production and the synthesis of nucleic acids (DNA and RNA), proteins, carbohydrates, and lipids (79). Magnesium also plays structural roles in bone, cell membranes, and chromosomes and is also required for various cellular processes, including ion transport across cell membranes, cell signaling, and cell migration (80).

The RDA of magnesium for children ages 4 to 8 years, which is 130 mg/day, was derived by extrapolating data from magnesium balance studies in older children (79). The RDA for boys and girls ages 9 to 13 years is 240 mg/day. This recommendation was based on data from magnesium balance studies in children of this age (81, 82). Good dietary sources of magnesium include nuts and green leafy vegetables because magnesium is part of chlorophyll — the green pigment in plants. Meats and milk have an intermediate magnesium content, with milk providing 24-39 mg per cup (79, 83). Refined foods generally have the lowest magnesium content. Analysis of data from the NHANES study found that US children ages 2 to 12 years who consumed three or more daily servings of whole grains had significantly increased magnesium intakes (84).

Sodium

The 2010 Dietary Guidelines for Americans recommend that children should limit their sodium intake to 1,500 mg/day to lower blood pressure and thus reduce their risk of cardiovascular and kidney diseases in adulthood (85). In 2004, the FNB set the AI for children by extrapolating from the adult AI using relative energy intakes. The AI for children 4 to 8 years is 1,000 mg/day, which translates to 2.5 grams of salt per day, and the AI for boys and girls 9 to 13 years is 1,200 mg/day, which translates to 3 grams of salt per day (86).

Zinc

The mineral zinc is essential for growth and development, immune function, neurological function, and reproduction. Zinc plays a number of catalytic, structural, and regulatory roles in cellular metabolism (see the article on Zinc). Zinc deficiency is a major public health concern and has been estimated to affect more than 2 billion people in less developed nations (87). Children are at increased risk for zinc deficiency, which can lead to delayed physical growth, impaired immunity, and possibly to delayed mental development. Mild forms of this mineral deficiency, which are common in both developing and developed nations, appear to have negative effects on growth and development (23, 88). However, the lack of a sensitive indicator of mild zinc deficiency hinders the scientific study of its health implications.

Mild zinc deficiency contributes to impaired physical growth in children (88, 89). Significant delays in linear growth and weight gain, known as growth retardation or failure to thrive, are common features of mild zinc deficiency in children. In the 1970s and 1980s, several randomized, placebo-controlled studies of zinc supplementation in young children with significant growth delays were conducted in Denver, Colorado. Modest zinc supplementation (5.7 mg/day) resulted in increased growth rates compared to placebo (89). More recently, a number of larger studies in developing countries observed similar results with modest zinc supplementation. A meta-analysis of growth data from zinc intervention trials recently confirmed the widespread occurrence of growth-limiting zinc deficiency in young children, especially in developing countries (90). Although the exact mechanism for the growth-limiting effects of zinc deficiency are not known, recent research indicates that zinc availability affects cell-signaling systems that coordinate the response to the growth-regulating hormone, insulin-like growth factor-1 (IGF-1) (91, 92).

Adequate zinc intake in children is essential in maintaining the integrity of the immune system (23, 93), and zinc deficiency is associated with increased susceptibility to a variety of infectious agents (94). The adverse effects of zinc deficiency on immune system function are likely to increase the susceptibility of children to infectious diarrhea, and persistent diarrhea contributes to zinc deficiency and malnutrition. It has been estimated that diarrheal diseases result in the deaths of about 3 million children each year (95). Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhea and to increase survival in a number of randomized controlled trials (96, 97). Recently, a meta-analysis of randomized controlled trials concluded that zinc supplementation reduces the frequency, severity, and duration of diarrheal episodes in children under five years of age (98). The World Health Organization and the United Nations Children's Fund currently recommend zinc supplementation as part of the treatment for diarrheal diseases in young children (99). Zinc supplementation may also reduce the incidence of lower respiratory infections, such as pneumonia. A pooled analysis of a number of studies in developing countries demonstrated a substantial reduction in the prevalence of pneumonia in children supplemented with zinc (100). A recent meta-analysis found that zinc supplementation reduced the incidence but not duration of pneumonia or respiratory tract illnesses in children under five years of age (98). Due to conflicting reports (101-104), it is not yet clear whether zinc supplementation has utility in treating childhood malaria.

Because a sensitive indicator of zinc nutritional status is not readily available, the RDA for zinc was based on a number of different indicators of zinc nutritional status and represents the daily intake likely to prevent deficiency in nearly all individuals in a specific age and gender group. The RDA for children ages 4 to 8 years is 5 mg/day, and the RDA for boys and girls ages 9 to 13 years is 8 mg/day (105). Shellfish, beef, and other red meats are rich sources of zinc. Nuts and legumes are relatively good plant sources of zinc. Zinc bioavailability (the fraction of zinc retained and used by the body) is relatively high in meat, eggs, and seafood because of the relative absence of compounds that inhibit zinc absorption and the presence of certain amino acids (cysteine and methionine) that enhance zinc absorption. The zinc in whole-grain products and plant proteins is less bioavailable due to their relatively high content of phytic acid, a compound that inhibits zinc absorption (106). The enzymatic action of yeast reduces the level of phytic acid in foods. Therefore, leavened whole-grain breads have more bioavailable zinc than unleavened whole-grain breads (105).

Other Nutrients

Choline

Choline can be synthesized by the body in small amounts, but dietary intake is needed to maintain health (107). Choline and its metabolites have a number of essential biological functions. Choline is used in the synthesis of specific phospholipids (i.e., phosphatidylcholine and sphingomyelin) that are structural components of cell membranes and also precursors for certain cell-signaling molecules. Choline is needed for myelination of nerves and is a precursor for acetylcholine, a neurotransmitter involved in muscle action, memory, and other functions (108-110). For more information about the role of choline in the body, see the article on Choline.

Due to the lack of data in children, intake recommendations for choline in children were extrapolated from adult recommendations using metabolic body weight, accounting for growth. The AI for children aged 4 to 8 years is 250 mg/day, and the AI for boys and girls aged 9 to 13 years is 375 mg/day (108). A number of foods contain choline, but eggs, meats, and milk are the primary sources in the American diet (111).

Essential fatty acids

α-Linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid, are considered essential fatty acids because they cannot be synthesized by humans. The long-chain omega-6 fatty acid, arachidonic acid (AA), can be synthesized from LA, and two long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can be synthesized from ALA (112). These polyunsaturated fatty acids have a number of biological activities that are generally important for the structure and function of cell membranes, vision, eicosanoid synthesis, regulation of gene expression, and nervous system function (see the article on Essential Fatty Acids).

Dietary intake recommendations for ALA and LA in children were based on median intakes of American children, a population where omega-3 and omega-6 fatty acid deficiencies are not observed. The AI of ALA for children ages 4 to 8 years is 0.9 g/day, while the AI of ALA for children ages 9 to 13 years is 1.2 and 1.0 g/day for boys and girls, respectively. The long-chain omega-3 fatty acids, EPA and DHA, can contribute to these intake recommendations. Flaxseeds, walnuts, and their oils are among the richest dietary sources of ALA, but canola oil is also an excellent source of ALA. Oily fish, such as salmon, tuna, trout, and sardines, are the major dietary source of EPA and DHA (113). The AI of LA for children ages 4 to 8 years is 10 g/day, while the AI of LA for boys and girls ages 9 to 13 years is 12 and 10 g/day, respectively. Sources of LA include vegetable oils, such as soybean, safflower, and corn oil, nuts, seeds, and some vegetables (see the article on Essential Fatty Acids).

Safety

The FNB sets a tolerable upper intake level (UL) for most micronutrients. The UL is the highest level of daily nutrient intake likely to pose no risk of adverse health effects in almost all individuals of a specified age group. This level applies to total daily intake from food, water, and supplements. Due to the potential for adverse effects, it is recommended that individuals not exceed the UL. Thus, individuals should use the UL as a guide to limit daily micronutrient intake, not as a recommended level of intake (114). **Table 3** lists the UL for children ages 4 to 8 years, and **Table 4** lists the UL for children ages 9 to 13 years.

Table 3. Dietary Reference Intakes Set by the FNB:
UL for Micronutrients During Childhood, Ages 4 to 8 Years

Micronutrient	Males and Females
Biotin	ND^a
Folate	400 μg/day^b
Niacin	15 mg/day^b
Pantothenic Acid	ND
Riboflavin	ND
Thiamin	ND
Vitamin A	900 μg/day (3,000 IU/day)^c
Vitamin B$_6$	40 mg/day
Vitamin B$_{12}$	ND
Vitamin C	650 mg/day
Vitamin D	75 μg/day (3,000 IU/day)
Vitamin E	300 mg/day (450 IU/day)^d
Vitamin K	ND
Calcium	2,500 mg/day
Chromium	ND
Copper	3,000 μg/day
Fluoride	2.2 mg/day
Iodine	300 μg/day
Iron	40 mg/day
Magnesium	110 mg/day^e
Manganese	3 mg/day
Molybdenum	600 μg/day
Phosphorus	3,000 mg/day
Potassium	ND
Selenium	150 μg/day
Sodium	ND
Zinc	12 mg/day
Choline^f	1,000 mg/day
α-Linolenic Acid^f	Not established
Linoleic Acid^f	Not established

^{a}ND, not determinable
^{b}Applies to the synthetic form in fortified foods and supplements
^{c}Applies only to preformed retinol
^{d}Applies to any form of supplemental α-tocopherol
^{e}Applies only to the supplemental form
^{f}Considered an essential nutrient, although not strictly a micronutrient

Table 4. Dietary Reference Intakes Set by the FNB:
UL for Micronutrients During Childhood, Ages 9 to 13 Years

Micronutrient	Males and Females
Biotin	ND^a
Folate	600 μg/day^b
Niacin	20 mg/day^b

Pantothenic Acid	ND
Riboflavin	ND
Thiamin	ND
Vitamin A	1,700 μg/day (5,667 IU/day)[c]
Vitamin B_6	60 mg/day
Vitamin B_{12}	ND
Vitamin C	1,200 mg/day
Vitamin D	100 μg/day (4,000 IU/day)
Vitamin E	600 mg/day (900 IU/day)[d]
Vitamin K	ND
Calcium	3,000 mg/day
Chromium	ND
Copper	5,000 μg/day
Fluoride	10 mg/day
Iodine	600 μg/day
Iron	40 mg/day
Magnesium	350 mg/day[e]
Manganese	6 mg/day
Molybdenum	1,100 μg/day
Phosphorus	4,000 mg/day
Potassium	ND
Selenium	280 μg/day
Sodium	ND
Zinc	23 mg/day
Choline[f]	2,000 mg/day
α-Linolenic Acid[f]	Not established
Linoleic Acid[f]	Not established

[a] ND, not determinable
[b] Applies to the synthetic form in fortified foods and supplements
[c] Applies only to preformed retinol
[d] Applies to any form of supplemental α-tocopherol
[e] Applies only to the supplemental form
[f] Considered an essential nutrient, although not strictly a micronutrient

Note that many children's multivitamin/mineral supplements on the market contain more than the RDA for several micronutrients when taken at the suggested dosage by age. Some even contain micronutrients (e.g., vitamin A, folic acid, copper, and zinc) at levels equivalent to the UL; this concern is for children younger than 9 years old. The Food and Nutrition Board of the Institute of Medicine recommends that daily nutrient intake from food and supplements not exceed the UL for each micronutrient. There is no evidence that consumption of micronutrients at or above the UL results in any health benefits in children, and the UL should not be exceeded except under medical supervision. Children often consume vitamin and mineral-fortified foods like cereal, and their total intake of certain micronutrients like vitamin A, folic acid, copper, and zinc from fortified foods, other dietary intake, and from supplements should be determined to ensure that the UL is not exceeded. It is also important to note that the daily values (DVs) listed on supplement labels in the US do not reflect the current intake recommendations (RDA or AI). Another caution is that many children's supplements look like candy but should never be labeled as such and, because of safety concerns, should be kept out of reach of children.

Conclusion

A healthy diet in children is important to provide nutrients that support optimum physical growth and cognitive development and to also establish healthy eating behaviors that lower risk of chronic diseases in adulthood. Although it is generally advised that micronutrients should be obtained from food, many children do not reach daily intake recommendations for select micronutrients, including vitamins A, C, D, and E, and some minerals, such as calcium and magnesium (37, 115).

Therefore, the Linus Pauling Institute recommends that children ages 4 to 13 years take a daily multivitamin/mineral supplement with 100% of the daily value (DV) for most vitamins and essential minerals, keeping the following suggestions in mind:

- Since the DV for vitamin A for those ages 4 and older (5,000 IU) is considerably higher than the current RDA for children ages 4 to 8 years (1,333 IU/day) and 9 to 13 years (2,000 IU/day), LPI recommends looking for a children's multivitamin/mineral supplement containing no more than 2,500 IU (750 μg) of vitamin A, of which at least 50% comes from β-carotene.
- In general, multivitamin/mineral supplements contain only a small percentage of the RDA for calcium and magnesium; therefore, intake of calcium and magnesium from dietary sources, such as low-fat milk, is important. If the RDAs for these minerals (1,000 and 1,300 mg/day for calcium and 130 and 240 mg/day for magnesium for children 4 to 8 years and 9 to 13 years, respectively) are not met through diet plus the multivitamin/mineral supplement, LPI recommends an additional, combined calcium-magnesium supplement for children.
- Because there are limited dietary sources of vitamin D and many children use sunscreens, which block skin synthesis of vitamin D, LPI recommends that all children ages 4 to 13 years should have a daily intake of 600 to 1,000 IU (15 to 25 μg) of vitamin D, consistent with the recommendations of the Endocrine Society (39). Given the average vitamin D content in the diets of children, supplementation may be necessary to meet this recommendation.

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DRIs for sodium and potassium updated 4/12/19

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Adolescents

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Micronutrient Requirements of Adolescents Ages 14 to 18 Years

Introduction

Adolescence — the transitional stage of development between childhood and adulthood — is associated with marked physical growth, reproductive maturation, and cognitive transformations. Physical changes begin in early adolescence during puberty, when sexual maturity is reached and reproduction is possible (1). Girls generally begin their adolescent growth spurt at an earlier age (9 years of age) than boys (11 years of age); the pubertal growth spurt lasts between two to four years, with the average rate of linear growth being 5-6 cm/year (2-2.4 in/year). Boys experience greater gains in height compared to girls because of a higher rate of growth and a longer growth spurt (2). Gains in linear growth are accompanied by increases in body weight and changes in body composition. Weight gain in girls typically happens six months following the greatest gains in linear growth, whereas weight gain in boys is usually coincident with increases in height. Throughout adolescence, boys gain more lean (fat-free) mass than girls, and girls experience greater increases in adiposity, which is required for normal menstruation (3). Moreover, approximately half of adult bone mass is obtained during adolescence (4), with boys experiencing greater gains in bone size and bone mass compared to girls (5).

In addition to physical growth, reproductive maturation occurs during adolescence. Maturation of the reproductive organs and development of secondary sexual characteristics, including facial hair in males and breast development in females, take place during puberty. Girls also experience menarche — the first occurrence of menstruation — during this developmental stage, typically following the peak period of gains in height and weight (6). Adolescence is further characterized by cognitive, emotional, and psychosocial development (2).

Good nutrition is needed to support the growth and developmental changes of adolescence. Undernutrition, in general, has been shown to delay the adolescent growth spurt (7). Overnutrition, a form of malnutrition where macronutrients (carbohydrates, fats, proteins) are supplied in excess of the body's needs, can lead to obesity and is a concern in industrialized nations. In the developed world, adolescents are increasingly consuming energy-rich, nutrient poor diets comprised of fast food, processed foods, and sugar-sweetened beverages (8-10). Studies have also shown that many adolescents do not come close to meeting intake recommendations for nutrient-rich foods, such as fruit, vegetables, and milk (11, 12). Together, these dietary behaviors place adolescents at increased risk for micronutrient deficiencies. This article discusses micronutrient requirements of adolescents aged 14 to 18 years, an age range that is used by the Food and Nutrition Board (FNB) of the US Institute of Medicine to establish dietary reference intakes. Due to limited data, many of the micronutrient intake recommendations for adolescents are extrapolated from recommendations for adults using a formula that accounts for metabolic body weight and growth (13), not unique physiological changes during adolescence. Metabolic body weight is determined by calculating the 0.75 power of body mass (body mass^0.75) (14). To account for growth, the equation used to derive a Recommended Dietary Allowance (RDA) or Adequate Intake (AI) involves an age group-specific growth factor (13). The FNB set different micronutrient intake recommendations for children 9 to 13 years, an age range that encompasses puberty and early stages of adolescence (15); discussion of the micronutrient requirements of younger children is included in a separate article (see Micronutrient Needs of Children Ages 9 to 13 Years).

Micronutrient Needs of Adolescents Aged 14 to 18 Years

For each micronutrient, the FNB sets an RDA or AI for adolescents aged 14 to 18 years. These recommendations are gender specific to account for the unique nutritional needs of males and females as they undergo the physiological changes of adolescence. **Table 1** lists the RDA for each micronutrient by gender. The RDA should be used in the planning of diets for individuals. A more detailed discussion of the requirements of certain micronutrients for adolescents can be found below.

Table 1. Dietary Reference Intakes Set by the FNB:
RDA for Micronutrients During Adolescence, Ages 14 to 18 Years, Per Day

Micronutrient	Males	Females
Biotin	25 μg (AI)	25 μg (AI)
Folate	400 μg[a]	400 μg[a]
Niacin	**16 mg[b]**	**14 mg[b]**
Pantothenic Acid	5 mg (AI)	5 mg (AI)
Riboflavin	**1.3 mg**	**1.0 mg**
Thiamin	**1.2 mg**	**1.0 mg**
Vitamin A	**900 μg (3,000 IU)[c]**	**700 μg (2,333 IU)[c]**
Vitamin B_6	**1.3 mg**	**1.2 mg**
Vitamin B_{12}	2.4 μg	2.4 μg
Vitamin C	**75 mg**	**65 mg**
Vitamin D	15 μg (600 IU)	15 μg (600 IU)
Vitamin E	15 mg (22.5 IU)[d]	15 mg (22.5 IU)[d]
Vitamin K	75 μg (AI)	75 μg (AI)
Calcium	1,300 mg	1,300 mg
Chromium	**35 μg (AI)**	**24 μg (AI)**
Copper	890 μg	890 μg
Fluoride	3 mg (AI)	3 mg (AI)
Iodine	150 μg	150 μg
Iron	**11 mg**	**15 mg**
Magnesium	**410 mg**	**360 mg**
Manganese	**2.2 mg (AI)**	**1.6 mg (AI)**
Molybdenum	43 μg	43 μg
Phosphorus	1,250 mg	1,250 mg
Potassium	3,000 mg (AI)	2,300 mg (AI)
Selenium	55 μg	55 μg
Sodium	1,500 mg (AI)	1,500 mg (AI)
Zinc	**11 mg**	**9 mg**

RDA, recommended dietary allowance; AI, adequate intake
[a] Dietary Folate Equivalents
[b] NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin
[c] Retinol Activity Equivalents
[d] α-Tocopherol

Vitamins

Vitamin A

Vitamin A is a fat-soluble vitamin that is essential for growth and development, normal vision, the expression of selected genes, immunity, and reproduction (16). Vitamin A deficiency in children and adolescents is a major public health problem worldwide, especially in less developed countries (17, 18). Even marginal or subclinical deficiencies in vitamin A may have adverse effects on bone growth and sexual maturation of adolescents (19). Because of its role in immunity, inadequate intake of this vitamin also increases risk for infectious diseases (20).

Studies in industrialized countries have reported inadequate intakes of vitamin A among adolescents (21-23). Serum retinol binding protein (RBP) concentrations have been shown to increase throughout the stages of puberty, indicating that vitamin A is needed for adolescent development (24). However, few vitamin A supplementation studies have been done in adolescents; most supplementation studies have included younger children who are more susceptible to vitamin A deficiency.

The RDA for vitamin A is based on the amount needed to ensure adequate stores (four months) of vitamin A in the body to support normal reproductive function, immune function, vitamin A-dependent gene expression, and vision (16). Vitamin A intake recommendations for adolescents were derived by extrapolating the recommendation for adults using metabolic body weight, accounting for growth. The RDA for adolescent boys aged 14 to 18 years is 900 μg per day of Retinol Activity Equivalents (RAE), which is 3,000 international units (IU); the RDA for adolescent girls aged 14 to 18 years is 700 μg of RAE, which is equivalent to 2,333 IU. For information on vitamin A content in foods, see the article on Vitamin A.

Vitamin B_6

Vitamin B_6 is required for heme synthesis and in the synthesis and metabolism of amino acids — the building blocks of proteins. Thus, the vitamin has obvious relevance to adolescent growth and health. Dietary intake recommendations of vitamin B_6 for adolescents were established by extrapolating data from adults, using metabolic body weight and accounting for growth. The RDA for boys aged 14 to 18 years is 1.3 mg/day, and the RDA for girls aged 14 to 18 years is 1.2 mg/day (25). Only a few studies have evaluated vitamin B_6 status specifically in adolescents. In an analysis of American adolescent girls (aged 12-16 years), mean dietary intake of vitamin B_6 was 1.2 mg/day; however, one-third of the girls not taking vitamin B_6-containing supplements had either marginal or deficient vitamin B_6 status (26). The same investigators found more than 40% vitamin B_6 inadequacy when a group of 112 adolescent girls (12- and 14-year-old) were followed for two years (27). Results of more recent studies have suggested that most American and European adolescents are meeting current intake recommendations for vitamin B_6 (28, 29), although a study in Canada found that more than half of adolescent males aged 14 to 18 years did not meet the Estimated Average Requirement (EAR) of 1.1 mg/day for vitamin B_6 (22). For information on dietary sources of the vitamin, see the article on Vitamin B_6.

Folate

The B vitamin, folate, is required as a coenzyme to mediate the transfer of one-carbon units. Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the endogenous synthesis and metabolism of nucleic acids (DNA and RNA) and amino acids (30, 31). Thus, folate has obvious importance in growth and development. Moreover, higher intakes of folate in adolescents have been linked to better academic achievement (32). Like other B vitamins, adolescent intake recommendations for folate were extrapolated from adult recommendations, using metabolic body weight and accounting for growth. The RDA for adolescents aged 14 to 18 years is 400 μg/day of dietary folate equivalents (33).

When considering naturally occurring folate in foods, results of a national survey indicate that almost 80% of individuals aged 2-18 years in the US have intakes below the EAR, which is 330 μg/day of dietary folate equivalents for adolescents aged 14-18 years. However, when accounting for intake from fortified foods, less than 5% of individuals in that age group have intakes below the EAR (34). The US Food and Drug Administration implemented legislation in 1998 requiring the fortification of all enriched grain products with folic acid (35). Globally, more than 50 countries have mandatory programs of wheat-flour fortification with folic acid, but flour fortification is not common in Europe (36). Dietary folate inadequacy is common among adolescents in European nations, especially girls (29).

Vitamin B_{12}

Vitamin B_{12} is needed for two types of reactions in the human body. One is transmethylation (methyl transfer between two molecules) that leads to the synthesis of the amino acid methionine from homocysteine. Methionine, in turn, is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, such as the methylation of sites within DNA and RNA (37). The second sort of reaction is isomerization (rearrangement of a molecule). Vitamin B_{12} acts as a coenzyme for methylmalonyl-CoA mutase to convert methylmalonyl-CoA to succinyl-CoA, an important step for the metabolism of proteins and lipids. Both transmethylation and isomerization reactions are essential for the metabolism of components of the myelin sheath of nerve cells and for the metabolism of neurotransmitters. Accordingly, vitamin B_{12} deficiency damages the myelin sheath covering cranial, spinal, and peripheral nerves, resulting in neurological damage (38, 39). The myelin sheath is the insulating layer of tissue made up of lipids and proteins that surrounds nerve fibers. This sheath acts as a conduit in an electrical system, allowing rapid and efficient transmission of nerve impulses (40). In some cases, neurologic symptoms caused by vitamin B_{12} deficiency can be reversed by vitamin treatment (38), but reversibility seems to be dependent upon the duration of the associated neurologic complications (41).

Although myelination primarily occurs during fetal development and early infancy, it continues through childhood, adolescence, and stages of early adulthood (42, 43). Because of the role of vitamin B_{12} in myelination and other metabolic processes, it is important for adolescents to meet dietary intake recommendations. The RDA of vitamin B_{12} for adolescent boys and girls aged 14 to 18 years is 2.4 μg/day (41), extrapolated from the recommendation for adults.

Vitamin B_{12} is naturally present only in animal products, such as meat, poultry, fish (including shellfish), and to a lesser extent in milk, but it is not generally present in plant products or yeast (44). Vitamin B_{12} deficiency has been reported in adolescents on very restricted or strict vegetarian diets (45, 46). Because vitamin B_{12} is stored in the liver, it may take three to six years for clinical symptoms to manifest (45). Thus, adolescents who have vegan diets need adequate intake from fortified foods or supplemental vitamin B_{12}.

Vitamin C

Vitamin C has a number of important roles during growth and development, including being required for the synthesis of collagen, carnitine, and neurotransmitters (47). Vitamin C is also a highly effective antioxidant and is important for immunity (see the article on Immunity). Further, vitamin C strongly enhances the absorption of nonheme iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}). Specifically, iron absorption is two- to three-fold higher with co-ingestion of 25 to 75 mg of vitamin C (48). This has special relevance to adolescent health, considering the fact that iron deficiency is prevalent among adolescents, especially girls (see the section on Iron). The RDA for adolescents aged 14 to 18 years, which was extrapolated from recommendations for adults based on relative body weight, is 75 mg/day and 65 mg/day of vitamin C for boys and girls, respectively (49).

Data on vitamin C intake among adolescents are limited, but a recent US national survey, the 2003-2004 National Health and Nutrition Examination Survey (NHANES), found that serum vitamin C concentrations of adolescents (aged 12-19 years) were lower in adolescents compared to younger children (6-11 years), and adolescent girls had higher levels than adolescent boys (50). In this analysis, 2.7% of adolescent boys and 3.9% of adolescent girls had overt vitamin C deficiency that could result in clinical symptoms of scurvy. A cross-sectional analysis of European adolescents (aged 12.5-17.5 years) also noted higher vitamin C status among adolescent girls compared to boys, and compared to the US survey, the prevalence of overt vitamin C deficiency was lower in European adolescents (51). For information on food sources, see the article on Vitamin C.

Vitamin D

Vitamin D is a fat-soluble vitamin that is essential for maintaining normal calcium metabolism and is therefore necessary for bone health. Severe vitamin D deficiency in infants and children results in the failure of bone to mineralize, leading to a condition known as rickets, but cases of rickets have also been reported during stages of puberty and adolescence (52-53). Rapidly growing bones are most severely affected by rickets. The growth plates of bones continue to enlarge, but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. Inadequate vitamin D during puberty and adolescence might prevent the attainment of peak bone mass and final height (54-56) and could possibly increase the risk of osteoporosis or other diseases in adulthood, but more studies on these associations are needed.

In 2010, the Food and Nutrition Board (FNB) of the Institute of Medicine set an RDA based on the amount of vitamin D needed for bone health and assuming minimal sun exposure; the RDA is 600 IU/day (15 μg/day) for adolescents aged 14 to 18 years. In the US, milk is voluntarily fortified with 400 IU (10 μg) of vitamin D per quart (946 mL); thus, adolescents would need to consume about 6 cups of milk daily to meet the RDA. Although fish is the best source of vitamin D in the diet, fortified foods and beverages are likely the major dietary source of vitamin D for US adolescents. In Canada, fortification of milk and margarine is mandatory, with milk containing 35-45 IU per 100 mL (331-426 IU per quart) and margarine containing 530 IU per 100 grams (57), but vitamin D fortification of foods is less common in European nations (58). In addition to diet, vitamin D can be endogenously synthesized in the skin upon exposure to ultraviolet-B radiation from sunlight; however, sunscreens effectively block skin synthesis of vitamin D and vitamin D synthesis is diminished in northern latitudes during winter (see the article on Vitamin D).

Analysis of data from NHANES 2005-2006 found that average total vitamin D intakes (from diet and supplements combined) in US adolescents (aged 14 to 18 years) were 6.9 μg/day (276 IU/day) for boys and 5.0 μg/day (200 IU/day) for girls — well below the current RDA. This analysis also found that 16% of adolescent boys and 27% of adolescent girls took vitamin D-containing supplements (59). Because sun exposure can substantially affect body vitamin D levels, measuring 25-hydroxyvitamin D — the major circulating form of vitamin D — is a more useful indicator of vitamin D status. However, studies assessing vitamin D status in adolescents have used various cutoffs to define vitamin D deficiency and insufficiency and there is no consensus of what level constitutes adequacy.

It is assumed that a dietary intake of 600 IU (15 μg)/day results in a serum 25-hydroxyvitamin D level of 20 ng/mL (50 nmol/L), which the FNB considers as the cut-off point for vitamin D adequacy (60). However, many researchers believe that higher levels may benefit health. NHANES found that more than 25% of US adolescents (12-19 years) had serum 25-hydroxyvitamin D concentrations lower than 20 ng/mL (50 nmol/L) and about 75% of adolescents had levels lower than 32 ng/mL (80 nmol/L) (61). Some studies have found a higher prevalence of vitamin D deficiency among European adolescents (19, 62). Ethnic and seasonal differences have also been reported, with higher levels in whites compared to blacks (61, 63) and in summertime compared to wintertime (62, 64, 65). Moreover, several studies have reported low vitamin D status among adolescents living in sunny climates (63, 66-68).

Oral vitamin D supplementation has been shown to improve vitamin D status among adolescents (69, 70), and one double-blind, placebo-controlled trial found that improvements in vitamin D status were accompanied by some musculoskeletal benefits in adolescent girls (70). Although more supplementation studies are needed, ensuring vitamin D adequacy throughout childhood and adolescence seems prudent. The Linus Pauling Institute recommends that adolescents aged 14 to 18 years should have a daily intake of 600 to 1,000 IU (15 to 25 μg) of vitamin D, consistent with the recommendations of the Endocrine Society (71). According to the Endocrine Society, at least 600 IU/day may be required to maximize bone health, and 1,000 IU/day may be needed to increase serum levels above 30 ng/mL (75 nmol/L) (71). Given the average vitamin D content of the diets of adolescents, supplementation may be necessary to meet this recommendation. The American Academy of Pediatrics currently suggests that all adolescents who do not get 400 IU/day of vitamin D through dietary sources should take 400 IU of supplemental vitamin D daily (72) — an amount that is typically found in multivitamin supplements.

Vitamin E

The RDA of vitamin E for adolescents, expressed as an amount of the α-tocopherol form of the vitamin, was based on extrapolations from intake recommendations for adults, accounting for differences in lean body mass and increased needs of growth during adolescence. The RDA is 15 mg/day (22.5 IU/day) for boys and girls ages 14 to 18 years (73). A US national survey, NHANES 1999-2000, found that adolescent boys and girls aged 14 to 18 years had average intakes of 7.5 mg/day and 5.7 mg/day of α-tocopherol, respectively. Moreover, 92% of adolescent boys and more than 99% of adolescent girls of this age group had daily intakes below the EAR of 12 mg/day (74). Vitamin E intake has been reported to be similarly low in adolescents in Spain (21), Switzerland (23), Brazil (75), France (76), and Germany (77). However, true vitamin E deficiency is rare and has been observed only in cases of severe malnutrition, genetic defects affecting the α-tocopherol protein, and fat malabsorption syndromes; see the article on Vitamin E.

Minerals

Calcium

About 99% of calcium in the body is found in bones and teeth (78). Adequate intake of calcium throughout childhood and adolescence is important for proper mineralization of growing bones, attainment of peak bone mass, and reduction of risk of bone fracture and osteoporosis in adulthood. Dietary intake recommendations for calcium in adolescents were established using a factorial method that summed average calcium accretion and calcium losses to urine, feces, and sweat and also adjusted for calcium absorption (60). Specifically, data used by the FNB to determine calcium accretion came from a recent longitudinal study in 642 Caucasian adolescents aged 14 to 18 years (79). The authors of this study estimated that the daily calcium requirement is higher in boys than girls; however, the FNB concluded that the differences were relatively small and it would be more practical to establish a single recommendation for all adolescents. Thus, the RDA was set at 1,300 mg/day; this level of calcium intake is expected to cover the needs of 97.5% of adolescents.

Many US adolescents have dietary calcium intakes below the RDA, with girls having lower intakes than boys. A recent analysis of data from NHANES 2003-2006, a US national survey, found that 42% of adolescent boys and only 10% of adolescent girls (14-18 years) had dietary calcium intakes above 1,300 mg/day. When accounting for use of calcium-containing supplements (19% and 24% of boys and girls, respectively; average supplemental intake of 142 and 182 mg/day of calcium in boys and girls, respectively), 42% of adolescent boys and only 13% of adolescent girls had total daily intakes above the current RDA (59). A recent publication that reviewed average calcium intake among adolescents in 23 nations found that boys generally have intakes of ~100-200 mg/day higher than girls and that many adolescents do not meet intake recommendations (80).

Dairy products, which provide about 72% of the calcium in the American diet (78), represent rich and absorbable sources of calcium. Milk contains 300 mg of calcium per cup; therefore, adolescents could meet the RDA for calcium by drinking 4.3 cups of low-fat milk daily. However, NHANES data show that US adolescents (12-19 years) on average consume only about 1 cup of milk daily (81). Lactose intolerance may prevent some adolescents from consuming milk, and consumption of soft drinks and other sweetened beverages might displace milk consumption in adolescents (82).

Certain vegetables and grains also provide calcium, but their bioavailability is lower compared with dairy. For more information on dietary sources of calcium and calcium bioavailability, see the article on Calcium. The Nutrition Facts label of packaged foods lists calcium content in one serving as a percent of the Daily Value (DV), with the DV being 1,000 mg. Since the RDA for adolescents is 1,300 mg/day, the percentage of the DV listed on the food label would be an overestimation of the percentage of the RDA. If adolescents do not meet the RDA through diet alone, LPI recommends supplemental calcium. Multivitamin/mineral supplements generally provide no more than 200 mg of calcium.

Iron

Iron is an essential component of hundreds of proteins and enzymes involved in various aspects of metabolism, including oxygen transport and storage, electron transport and energy metabolism, antioxidant and beneficial pro-oxidant functions, oxygen sensing, and DNA synthesis (44, 83-85); see the article on Iron. Iron deficiency, which is the most common nutritional deficiency in the world, is a major public health problem, especially in developing nations, but it is also prevalent in industrialized nations, notably in women of childbearing age. Severe iron deficiency leads to iron-deficiency anemia; anemia affects more than 30% of the global population (2 billion people) (81). Adolescents have increased requirements for iron due to rapid growth. In particular, adolescent girls are at a heightened risk of iron deficiency due to inadequate intake of dietary iron, especially heme iron; increased demands of growth; and iron loss that occurs with menstruation. Following puberty, adolescent girls have lower iron stores compared to adolescent boys (87).

In addition to the negative effects of iron deficiency on physical growth, iron deficiency during adolescence may impair immunity (see the article on Nutrition and Immunity) as well as cognition. Iron is needed for proper development of oligodendrocytes (the brain cells that produce myelin) (88), and the mineral is also a required cofactor for several enzymes that synthesize neurotransmitters (89). Iron deficiency — even levels not associated with anemia — during important stages of brain development, such as adolescence, may have detrimental consequences. A double-blind, placebo-controlled trial in 73 adolescent girls (aged 13-18 years) with non-anemic iron deficiency found that high-dose iron supplementation (260 mg/day of elemental iron) for eight weeks resulted in greater improvement in verbal learning but not in other cognitive domains (90). Another study reported that one-month iron supplementation beyond that included in a prenatal vitamin improved some measures of attention and short-term memory in young pregnant women (aged 14-24 years) without severe iron deficiency (91). Clinical trials of iron supplementation to date have been mostly done in other age groups; large, well-designed trials in adolescents are needed to determine the effects of iron supplementation on cognition.

Dietary intake recommendations for adolescents were based on a factorial modeling approach that accounts for the amount of iron needed to replace basal losses (losses in urine, feces, and sweat), iron requirements associated with growth (increases in hemoglobin and iron content of tissues), and iron losses associated with menstruation in girls. The intake recommendations also account for average bioavailability (the fraction of iron retained and used by the body) of dietary iron for this age group (92). The RDA of iron is 11 mg/day for adolescent boys and 15 mg/day for adolescent girls. A US national survey, NHANES 2001-2002, found that average dietary intake of iron was 19.1 mg/day in adolescent boys and 13.3 mg/day in adolescent girls; however, 16% of adolescent girls had intakes below the EAR of 7.9 mg/day. Because several different criteria have been used to identify iron deficiency, it is difficult to report the prevalence of iron deficiency among adolescents.

The amount of bioavailable iron in food (or supplements) is influenced by the iron nutritional status of the individual and also by the form of iron (heme or nonheme). Individuals who are anemic or iron deficient absorb a larger percentage of the iron they consume (especially nonheme iron) than individuals who are not anemic and have sufficient iron stores (94, 95). Heme iron, found in meat, poultry, and fish, is more readily absorbed, and its absorption is less affected by other dietary factors than nonheme iron — the form found in plants, dairy products, fortified foods, and supplements. Although heme iron generally accounts for only 10-15% of the iron found in the diet, it may provide up to one third of total absorbed dietary iron (83, 95). The absorption of nonheme iron is strongly influenced by enhancers and inhibitors present in the same meal. For instance, vitamin C strongly enhances the absorption of nonheme iron by reducing dietary ferric iron (Fe3+) to ferrous iron (Fe2+) and forming an absorbable, iron-ascorbic acid complex. Organic acids, such as citric, malic, tartaric, and lactic acids, also enhance nonheme iron absorption. Further, consumption of meat, poultry, and fish enhance nonheme iron absorption, but the mechanism for this increase in absorption is not clear (92, 94). Inhibitors of nonheme iron absorption include phytic acid, which is present in legumes, grains, and rice. Polyphenols found in some fruit, vegetables, coffee, tea, wines, and spices can also markedly inhibit the absorption of nonheme iron, but this effect is reduced by the presence of vitamin C (92, 96). Soy protein, such as that found in tofu, has an inhibitory effect on iron absorption that is independent of its phytic acid content (92).

Magnesium

The mineral magnesium is involved in more than 300 essential metabolic reactions that are generally involved in energy production and the synthesis of nucleic acids (DNA and RNA), proteins, carbohydrates, and lipids (97). Magnesium also plays structural roles in bone, cell membranes, and chromosomes and is also required for various cellular processes, including ion transport across cell membranes, cell signaling, and cell migration (98).

The RDA of magnesium for those aged 14 to 18 years, 410 mg/day for boys and 360 mg/day for girls, was derived from results of balance studies in adolescents. Good dietary sources of magnesium include nuts, and green leafy vegetables because magnesium is part of chlorophyll — the green pigment in plants. Meats and milk have an intermediate magnesium content, with milk providing 24-39 mg per cup (97). Refined foods generally have the lowest magnesium content. Although data are limited, some studies have found that a large percentage of adolescents have magnesium intakes below recommended levels (100-102). Data on magnesium intake among adolescents are lacking. In an analysis of NHANES data, US adolescents who consumed milk (plain or flavored) had higher daily magnesium intakes than adolescents who did not drink milk (103). However, NHANES data show that US adolescents (12-19 years) on average only consume about 1 cup of milk daily (81). Low-fat milk, nuts, whole grains, and green leafy vegetables are important sources of magnesium for adolescents. If adolescents do not meet the RDA through dietary sources, LPI recommends a combined magnesium-calcium supplement.

Potassium

Potassium is required for maintenance of cellular membrane potential and thus for nerve impulse transmission, muscle contraction, and heart function. In general, adolescents have low intakes of fruit, vegetables, and dairy products (104-106) — foods that are rich in potassium. Low intakes of potassium, coupled with high intakes of sodium (see section on Sodium), have been linked to elevations in blood pressure and a heightened risk of hypertension and stroke later in life (see the article on Potassium). In a study that followed 2,368 adolescent girls for nine years, lower intakes of potassium were associated with a higher incidence of hypertension (107). Fruit, vegetables, low-fat milk, and nuts are all good sources of potassium, and increasing intake of these foods during adolescence should help regulate blood pressure and may decrease risk of chronic disease during adulthood.

Sodium

In 2019, the FNB set the AI for adolescents by extrapolating from the adult AI using relative energy intakes; however, since energy intakes of adolescents are similar to that of adults, the recommendations are identical: 1,500 mg/day of sodium (108). The 2010 Dietary Guidelines for Americans recommend limiting sodium intake to 1,500 mg/day to lower blood pressure and thus reduce risk of cardiovascular disease and kidney diseases in adulthood. However, daily sodium intake in US adolescents (aged 12-19 years) is 3,000 mg in girls and 4,000 mg/day in boys (109). Low-sodium interventions in adolescents have shown some improvement in blood pressure, but compliance to such a diet is problematic (110, 111).

Zinc

The mineral zinc is essential for growth and development, immune function, neurological function, and reproduction. Zinc plays a number of catalytic, structural, and regulatory roles in cellular metabolism (see the article on Zinc). Zinc deficiency, which is estimated to affect more than 2 billion people in less developed nations (112), can retard normal growth, impair cognitive development, and delay sexual maturation (113, 114). Adolescents are at increased risk of zinc deficiency due to the demands of growth (115). Mild zinc deficiency, which is common in both the developing and developed world, may also have negative effects on growth and development (47, 116); however, the lack of a sensitive indicator of mild zinc deficiency hinders the scientific study of its health implications.

Because a sensitive indicator of zinc nutritional status is not readily available, the RDA for zinc was based on a number of different indicators of zinc nutritional status and represents the daily intake likely to prevent deficiency in nearly all individuals in a specific age and gender group. The RDA for adolescent boys and girls, aged 14 to 18 years, is 11 mg/day and 9 mg/day, respectively (113). A US national survey, NHANES 2001-2002, found that average dietary intake of zinc was 15.1 mg/day in adolescent boys and 9.5 mg/day in adolescent girls; only 4% of adolescent boys had intakes less than the EAR (8.5 mg/day), but 26% of adolescent girls had intakes less than the EAR (7.3 mg/day).

Shellfish, beef, and other red meats are rich sources of zinc; nuts and legumes are relatively good plant sources of zinc. Zinc bioavailability (the fraction of zinc retained and used by the body) is relatively high in meat, eggs, and seafood because of the relative absence of compounds that inhibit zinc absorption and the presence of certain amino acids (cysteine and methionine) that enhance zinc absorption. However, the zinc in whole-grain products and plant proteins is less bioavailable due to their relatively high content of phytic acid, a compound that inhibits zinc absorption (117). The enzymatic action of yeast reduces the level of phytic acid in foods. Therefore, leavened whole-grain breads have more bioavailable zinc than unleavened whole-grain breads (113).

Adolescent Pregnancy

Pregnancy during adolescence — a time when the girl is still growing herself — has been associated with increased risk of miscarriage, prematurity, low birth weight infants (<2,500 grams), and increased maternal and neonatal mortality (2, 118-119). Pregnant adolescents are also at a heightened risk for pregnancy-related complications, including pregnancy-induced hypertension and anemia (119). Because they are growing themselves, it is extremely important for pregnant adolescents to meet dietary intake recommendations. Recommendations for some key micronutrients needed for adolescent growth, including calcium, magnesium, phosphorus, and zinc, are higher than those for older pregnant women; see the discussion of Micronutrient Requirements During Pregnancy in a separate article. Pregnant adolescents are at increased risk for select micronutrient inadequacies, especially iron, zinc, calcium, magnesium, folate, vitamin B_6, vitamin D, and vitamin E (2, 120-121). Adequate nutrition is important not only for a healthy pregnancy outcome but also for the overall and skeletal health of the adolescent. A recent cross-sectional study of 719 postmenopausal women associated their pregnancy during adolescence with lower bone mineral density at several sites and a two-fold higher risk of osteoporosis compared to women without a history of adolescent pregnancy (122). However, it is not known whether adequate calcium intake during adolescent pregnancy might prevent age-related declines in bone mineral density or osteoporosis.

Safety

The FNB establishes a tolerable upper intake level (UL) for most micronutrients. The UL is the highest level of daily nutrient intake likely to pose no risk of adverse health effects in almost all individuals of a specified age group. This level applies to total daily intake from food, water, and supplements. Due to the potential for adverse effects, it is recommended that individuals not exceed the UL. Thus, individuals should use the UL as a guide to limit daily micronutrient intake, not as a recommended level of intake (123). There is no evidence that consumption of micronutrients at or above the UL results in any health benefits for adolescents, and the UL should not be exceeded except under medical supervision. **Table 2** lists the UL for adolescents.

Table 2. Dietary Reference Intakes Set by the FNB: UL for Micronutrients During Adolescence, Ages 14 to 18 Years, Per Day

Micronutrient	Males and Females
Biotin	ND[a]
Folate	800 μg[b]
Niacin	30 mg[b]
Pantothenic Acid	ND
Riboflavin	ND
Thiamin	ND
Vitamin A	2,800 μg (9,333 IU)[c]
Vitamin B_6	80 mg
Vitamin B_{12}	ND
Vitamin C	1,800 mg
Vitamin D	100 μg (4,000 IU)
Vitamin E	800 mg (1,200 IU)[d]
Vitamin K	ND
Calcium	3,000 mg
Chromium	ND
Copper	8,000 μg
Fluoride	10 mg
Iodine	900 μg
Iron	45 mg
Magnesium	350 mg[e]
Manganese	9 mg
Molybdenum	1.7 mg
Phosphorus	4,000 mg
Potassium	ND
Selenium	400 μg
Sodium	2,300 mg
Zinc	34 mg

[a] ND, not determinable
[b] Applies to the synthetic form in fortified foods and supplements
[c] Applies only to preformed retinol
[d] Applies to any form of supplemental α-tocopherol

[e]Applies only to the supplemental form

Conclusion

A healthy diet throughout puberty and adolescence is important to provide nutrients that support optimal physical growth and cognitive development. Although it is generally advised that micronutrients should be obtained from food, many adolescents do not reach daily intake recommendations for select micronutrients from diet alone. Therefore, the Linus Pauling Institute recommends that adolescents aged 14 to 18 years take a daily multivitamin/mineral supplement with 100% of the daily value (DV) for most vitamins and essential minerals, keeping the following suggestions in mind:

- Since the DV for vitamin A for those ages 4 and older (5,000 IU) is considerably higher than the current RDA for adolescents aged 14 to 18 years (3,000 IU/day for boys and 2,333 IU/day for girls), LPI recommends looking for a multivitamin/mineral supplement that provides no more than 2,500 IU (750 µg) of preformed vitamin A (usually labeled as vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene.
- In general, multivitamin/mineral supplements contain only a small percentage of the RDA for calcium and magnesium; therefore, intake of calcium and magnesium from dietary sources, such as low-fat milk, is important. If the RDAs for these minerals (1,300 mg/day for calcium; 410 and 360 mg/day for magnesium for adolescent boys and girls, respectively) are not met through diet plus the multivitamin/mineral supplement, LPI recommends an additional, combined calcium-magnesium supplement for adolescents.
- Because there are limited dietary sources of vitamin D and many adolescents use sunscreens, which block skin synthesis of vitamin D, LPI recommends that all adolescents aged 14 to 18 years should have a daily intake of 600 to 1,000 IU (15 to 25 µg) of vitamin D, consistent with the recommendations of the Endocrine Society (71). Given the average vitamin D content in the diets of adolescents, supplementation may be necessary to meet this recommendation.

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DRIs for sodium and potassium updated 4/12/19 Copyright 2012-2023 Linus Pauling Institute

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Micronutrient Needs During Pregnancy and Lactation

Introduction

Nutrient needs during the life stages of pregnancy and lactation are increased relative to women who are not pregnant or lactating. Mathematical models predict that energy requirements increase by an estimated 300 kcal/day during the second and third trimesters of pregnancy and by 500 kcal/day during lactation (1). In practice, most women will require only approximately 200 additional kcal/day due to reduced levels of physical activity during pregnancy and to increased lipolysis of fat stores during breast-feeding [personal communication with Dr. Berthold Koletzko]. Relative to the increased energy requirement, the requirements for many micronutrients (vitamins and nutritionally essential minerals) are even higher during pregnancy and lactation; this article discusses micronutrient needs during these life stages.

Micronutrient Requirements During Pregnancy

Pregnancy is associated with increased nutritional needs due to physiologic changes of the woman and the metabolic demands of the embryo/fetus. Proper maternal nutrition during pregnancy is thus imperative for the health of both the woman and the offspring. Maternal malnutrition during pregnancy has been associated with adverse outcomes, including increased risk of maternal and infant mortality, as well as low-birth-weight newborns (<2,500 grams) — a measure that accounts for preterm birth and intrauterine growth restriction of the fetus (2, 3). Select nutrient deficiencies have also been linked to congenital anomalies and birth defects. In addition, gestational undernutrition has been implicated in increasing the offspring's susceptibility to chronic disease (i.e., type 2 diabetes, hypertension, coronary heart disease, and stroke) in adulthood, a phenomenon sometimes called Barker's hypothesis, the thrifty phenotype hypothesis, or the fetal origin of adult disease hypothesis (4, 5). Maternal undernutrition often refers to malnutrition caused by insufficient caloric (energy) intake from macronutrients (carbohydrates, proteins, and lipids) during pregnancy, but micronutrient deficiencies are also a form of undernutrition. Multiple micronutrient deficiencies commonly co-exist in pregnant women (6).

Daily requirements for many micronutrients during pregnancy are higher to meet the physiologic changes and increased nutritional needs of pregnancy. Good nutritional status prior to conception is also important for a healthy pregnancy. For instance, folic acid supplementation during the periconceptional period (about one month before conception until the end of the first trimester) dramatically reduces the incidence of devastating birth defects called neural tube defects (see Folate below). Thus, folic acid supplementation (at least 400 µg/day) is recommended for all women capable of becoming pregnant (7-9). A well-balanced diet throughout pregnancy is necessary to supply the developing embryo/fetus with micronutrients. In addition to folic acid supplementation, iron supplementation is generally needed to meet the increased demands for this mineral during pregnancy (see the section on Iron below).

The Food and Nutrition Board (FNB) of the Institute of Medicine establishes life-stage specific dietary reference intakes (DRIs) for each micronutrient; these reference values should be used to plan and assess dietary intakes in healthy people (10, 11). The DRIs include the estimated average requirement (EAR), the recommended dietary allowance (RDA), the adequate intake (AI), and the tolerable upper intake level (UL). The RDA, which is the average daily dietary intake level of a nutrient sufficient to meet the requirements of almost all (97.5%) healthy individuals in a specific life stage and gender group, should be used in the planning of diets for individuals (12). The FNB establishes an AI when an RDA cannot be determined. The below recommendations are specific to the life stages of pregnancy and lactation. For most micronutrients, the RDA or AI for pregnant women is increased compared to nonpregnant women of the same age (**Table 1**). The discussion below largely focuses on these recommendations for select micronutrients during pregnancy but also notes major concerns for micronutrient toxicity or teratogenicity. The UL is the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals of a specified life stage. For the UL for each micronutrient during pregnancy, see **Table 2**.

Table 1. RDA for Micronutrients During Pregnancy

Micronutrient	Age	RDA
Biotin	14-50 years	30 µg/day (AI)
Folate	14-50 years	600 µg/day[a]
Niacin	14-50 years	18 mg/day[b]
Pantothenic Acid	14-50 years	6 mg/day (AI)
Riboflavin	14-50 years	1.4 mg/day
Thiamin	14-50 years	1.4 mg/day
Vitamin A	14-18 years	750 µg (2,500 IU)/day[c]
	19-50 years	770 µg (2,567 IU)/day[c]
Vitamin B_6	14-50 years	1.9 mg/day
Vitamin B_{12}	14-50 years	2.6 µg/day
Vitamin C	14-18 years	80 mg/day
	19-50 years	85 mg/day
Vitamin D	14-50 years	15 µg (600 IU)/day
Vitamin E	14-50 years	15 mg (22.5 IU)/day[d]
Vitamin K	14-18 years	75 µg/day (AI)
	19-50 years	90 µg/day (AI)
Calcium	14-18 years	1,300 mg/day
	19-50 years	1,000 mg/day
Chromium	14-18 years	29 µg/day (AI)
	19-50 years	30 µg/day (AI)
Copper	14-50 years	1 mg/day
Fluoride	14-50 years	3 mg/day (AI)
Iodine	14-50 years	220 µg/day
Iron	14-50 years	27 mg/day
Magnesium	14-18 years	400 mg/day
	19-30 years	350 mg/day
	31-50 years	360 mg/day
Manganese	14-50 years	2 mg/day (AI)
Molybdenum	14-50 years	50 µg/day
Phosphorus	14-18 years	1,250 mg/day
	19-50 years	700 mg/day
Potassium	14-18 years	2,600 mg/day (AI)
	19-50 years	2,900 mg/day (AI)
Selenium	14-50 years	60 µg/day
Sodium	14-50 years	1,500 mg/day (AI)
Zinc	14-18 years	12 mg/day
	19-50 years	11 mg/day
Choline[e]	14-50 years	450 mg/day (AI)

AI, adequate intake
[a]Dietary Folate Equivalents
[b]NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin
[c]Retinol Activity Equivalents
[d]α-Tocopherol
[e]Considered an essential nutrient, although not strictly a micronutrient

Vitamins

Biotin

Biotin is needed as a cofactor for carboxylase enzymes and for the attachment of biotin to molecules, such as proteins, in a process known as "biotinylation" (13). Rapidly dividing cells of the developing fetus require the vitamin for synthesis of essential carboxylase enzymes and for histone biotinylation. Although maternal biotin deficiency in certain strains of mice causes malformations in the offspring, namely cleft palate and limb shortening (14, 15), a link between biotin deficiency and birth defects in humans has not been observed.

Experimentally induced, marginal biotin deficiency results in the increased urinary excretion of 3-hydroxyisovaleric acid (3-HIA) and decreased urinary excretion of biotin and the biotin catabolites, bisnorbiotin (BNB) and biotin disulfoxide (BSO) (16, 17). Abnormally elevated urinary excretion of 3-HIA and abnormally decreased urinary excretion of biotin are the most extensively validated biomarkers of low biotin status (18).

Two observational studies have reported that there is an increased urinary excretion of 3-HIA during pregnancy, though other indices of biotin status were not consistently altered (19, 20). Similarly, a 2014 feeding study in which all subjects consumed a mixed diet with a known amount of biotin (average daily intake, 57 µg biotin/day), urinary 3-HIA excretion was higher in pregnant compared to nonpregnant women, while urinary biotin and BNB excretion did not differ between the groups (21). Supplementation with biotin (300 µg/day for 14 days) reduced urinary 3-HIA and increased urinary biotin excretion in pregnant women with elevated 3-HIA; however, this intervention did the same for nonpregnant controls considered to have normal biotin status (22).

Elevated urinary excretion of 3-HIA during pregnancy could be due to several possibilities. Some suggest that it reflects marginal biotin deficiency and the need for more biotin during pregnancy (23, 24). Alternatively, increased 3-HIA in isolation could reflect altered leucine metabolism or renal handling of organic acids during pregnancy (18).

At this time, the AI for biotin (30 µg/day) is the same for pregnant and nonpregnant women. Biotin is widespread in food, though its concentration varies substantially (see the article on Biotin). Based on dietary intake data from the National Health and Nutrition Examination Survey (NHANES) II (18, 25) and the above-mentioned feeding study (21), a typical mixed diet provides approximately 40 to 60 µg of biotin/day.

Folate

The terms folate and folic acid are often used interchangeably, but folic acid is the synthetic form of the vitamin that is only found in fortified food and supplements. Folic acid is more bioavailable than folate from food (see the article on Folate); folic acid is converted to biologically active forms of folate in the body. Folate is needed for amino acid and nucleic acid (DNA and RNA) metabolism. Adequate folate status is critical to embryonic and fetal growth — developmental stages characterized by accelerated cell division. In particular, folate is needed for closure of the neural tube early in pregnancy, and periconceptional supplementation with folic acid has been shown to dramatically reduce the incidence of neural tube defects (NTDs) (reviewed in 26 and 27). NTDs are devastating congenital malformations that can occur as either anencephaly or spina bifida. Because these birth defects occur between 21 to 27 days after conception (28), often before many women recognize their pregnancy, it is recommended in the US that all women capable of becoming pregnant take supplemental folic acid (7).

A recent systematic review of five trials, including 7,391 women, found that periconceptional folic acid supplementation, alone or with other micronutrients, was associated with a 69% lower risk of NTDs (risk ratio (RR), 0.31; 95% confidence interval (CI), 0.17 to 0.58) (29). The RDA for pregnant women is 600 µg/day of dietary folate equivalents (DFE), which is equivalent to 300 µg/day of synthetic folic acid on an empty stomach or 353 µg/day of synthetic folic acid with a meal (see the article on Folate). The US Preventive Services Task Force recommends a daily supplement of 400-800 µg of folic acid, in addition to consuming food folate from a varied diet, for all women planning or capable of pregnancy (9). Supplemental folic acid use at the higher end of this suggested range has been recommended by some (27, 30), and 800 µg/day from supplements plus dietary intake is safe for women of childbearing age.

Multivitamin/mineral supplements marketed in the US commonly contain 400 µg of folic acid, and many prenatal supplements marketed in the US contain 800 µg of folic acid. Folic acid may also be present in the food supply: several countries have programs of mandatory folic acid fortification to help reduce the incidence of NTDs; for example, the US FDA implemented legislation in 1998 requiring the fortification of all enriched grain products with folic acid at a level of 140 µg folic acid/100 g of product (31). Mandatory fortification in the US has resulted in a 28 percent reduction (an estimated 1,326 births/year) in the prevalence of NTDs (32).

Doses greater than 1 mg/day of folic acid are used pharmacologically to treat hyperhomocysteinemia and to prevent reoccurrence of NTDs (33). Women who have had a previous NTD-affected pregnancy may be advised to consume up to 4 to 5 mg/day (4,000 to 5,000 µg/day) of folic acid if they are planning a pregnancy, but this level of supplementation should be prescribed by their medical provider (see the CDC recommendations and the World Health Organization [WHO] guidelines).

A new form of folate, 5-methyltetrahydrofolate (5-MTHF), has been proposed as an alternative to folic acid. 5-MTHF is less likely to mask a severe vitamin B_{12} deficiency, exhibits lower interaction potential with antimalarial drugs, and may be preferable for women with an MTHFR polymorphism (26, 34). While the effect of 5-MTHF supplementation on NTDs has not yet been evaluated, it is at least as effective as folic acid at raising red blood cell folate status and reducing homocysteine concentrations in nonpregnant healthy young women (35-38) and lactating women (39).

Inadequate folate status may also be linked to other birth defects, such as cleft lip, cleft palate, and limb malformations, but there are insufficient data to evaluate the effect of folic acid supplementation on these outcomes (26). However, results of some case-control studies (40-44) and controlled trials (45, 46) have suggested that periconceptional supplementation with a multivitamin containing folic acid may protect against congenital cardiovascular malformations, especially conotruncal (outflow tract) and ventricular septal defects. A 2006 systematic review and meta-analysis concluded that such supplementation was associated with a 22% lower risk of cardiovascular defects in case-control studies and a 39% lower risk in cohort studies and randomized controlled trials (47).

Impaired folate status during pregnancy may also be associated with other adverse pregnancy outcomes. Elevated blood homocysteine concentrations, considered an indicator of functional folate deficiency, have been associated with increased risk of preeclampsia, premature delivery, low placental weight, low birth weight, very low birth weight (<1,500 grams), small for gestational age, neural tube defects (NTDs), and stillbirth (48-50). Thus, it is reasonable to maintain folic acid supplementation throughout pregnancy, even after closure of the neural tube, in order to decrease the risk of other potential problems during pregnancy.

Riboflavin

Riboflavin is a component of flavocoenzymes involved in energy metabolism, as well as antioxidant functions. The Food and Nutrition Board of the Institute of Medicine recommends that all pregnant women consume 1.4 mg of riboflavin daily. Riboflavin deficiency has been implicated in preeclampsia — a pregnancy-associated complication characterized by elevated blood pressure, protein in the urine, and edema (significant swelling). Preeclampsia is estimated to affect 2%-8% of all pregnancies (51), and about 5% of women with preeclampsia progress to eclampsia, a significant cause of maternal death (52). Eclampsia is characterized by seizures, in addition to high blood pressure and increased risk of hemorrhage (severe bleeding) (52). Although the specific causes of preeclampsia are not known, decreased intracellular concentrations of flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress, and interfere with nitric oxide release and thus blood vessel dilation. All of these changes have been associated with preeclampsia, but there have been few studies on the association of riboflavin nutritional status and the condition. A study in 154 pregnant women at high risk for preeclampsia found that those who were riboflavin deficient were 4.7 times more likely to develop preeclampsia than those who had adequate riboflavin nutritional status (53). However, a small randomized, double-blind, placebo-controlled trial in 450 pregnant women at high risk for preeclampsia found that supplementation with 15 mg of riboflavin daily did not prevent the condition (54).

Vitamin A

Adequate maternal status of vitamin A is critical for a healthy pregnancy. Forms of the vitamin, known as retinoids, are involved in the regulation of gene expression, cellular proliferation and differentiation, growth and development, vision, and immunity (see the article on Vitamin A). The retinoids, retinol and retinoic acid, are essential for embryonic and fetal development (55); for example, retinoic acid functions in forming the heart, eyes, ears, and limbs (56). Animal studies demonstrate that severe vitamin A deficiency or excess during critical periods of development results in a spectrum of malformations, especially affecting craniofacial structures, limbs, and visceral organs (57).

Forms of vitamin A are also necessary for maternal health. Vitamin A deficiency during pregnancy has been linked to impaired immunity, increased susceptibility to infection, increased risk of maternal morbidity and mortality (58-61), and night blindness (62). Vitamin A deficiency may exacerbate iron-deficiency anemia (see section on Iron below); co-supplementation with vitamin A and iron seems to ameliorate anemia more effectively than either micronutrient supplement alone (63). Vitamin A deficiency is a major public health problem in developing nations, where availability of foods containing preformed vitamin A (retinol) and provitamin A carotenoids is limited (for information on food sources of vitamin A, see the article on Vitamin A). The RDA during pregnancy is 750 to 770 µg/day (2,500 to 2,567 IU/day) of preformed vitamin A (see **Table 1** above).

Although normal embryonic and fetal development require sufficient maternal vitamin A intake, consumption of excess preformed vitamin A during pregnancy causes birth defects. An increased risk of vitamin A-associated birth defects has not been observed at supplemental doses below 3,000 µg (10,000 IU)/day of preformed vitamin (64). However, because a number of foods in the US are fortified with preformed vitamin A, the Linus Pauling Institute recommends that pregnant women avoid multivitamin or prenatal supplements that contain more than 750 µg (2,500 IU) of preformed vitamin A. Vitamin A from β-carotene is not known to increase the risk of birth defects (58), although the safety of high-dose β-carotene supplements in pregnancy has not been well studied. Moreover, pharmacological use of retinoids by pregnant women causes serious birth defects; thus, tretinate, isotretinoin (Accutane), and other retinoids should not be used during pregnancy or if there is a possibility of becoming pregnant (65). Use of tretinoin (Retin-A), a topically applied retinoid, exhibits very low systemic absorption, but is not recommended during pregnancy due to possible risks (66). It is important to note that retinoids tend to be very long acting; birth defects have been reported to occur months after discontinuing retinoid therapy (57). Retinoids are used therapeutically to treat retinitis pigmentosa, acute promyelocytic leukemia, various skin diseases, and other conditions.

Vitamin B_6

Vitamin B_6 has diverse roles in the body, including nervous system function, red blood cell formation and function, steroid hormone function, nucleic acid synthesis, and niacin formation. Pyridoxal, pyridoxine, and pyridoxamine are three forms of the vitamin. The RDA for vitamin B_6 during pregnancy is 1.9 mg/day. Vitamin B_6 has been used since the 1940s to treat nausea during pregnancy. The results of two double-blind, placebo-controlled trials that used 25 mg of pyridoxine every eight hours for three days (67) or 10 mg of pyridoxine every eight hours for five days (68) suggest that vitamin B_6 may be beneficial in alleviating morning sickness. Each study found a slight but significant reduction in nausea or vomiting in pregnant women. A third randomized trial compared high-dose (10 mg/day) and low-dose (1.28 mg/day) vitamin B_6 in 60 pregnant women experiencing nausea and/or vomiting prior to the twelfth week of gestation (69). After two weeks, nausea and vomiting scores decreased to an equal extent in both supplementation groups. A 2014 pooled analysis indicates that supplemental vitamin B_6 alone may be effective in alleviating nausea, but not vomiting, during pregnancy (70). Vitamin B_6 at the above-mentioned dosages is considered safe during pregnancy, and the vitamin has been used in pregnant women without any evidence of fetal harm (68, 71).

Vitamin B_6 was included in the medication Bendectin (a delayed-release formulation of 10 mg doxylamine succinate [an antihistamine] and 10 mg pyridoxine hydrochloride [vitamin B_6]), which was prescribed for the treatment of morning sickness and later withdrawn from the market in 1983 due to unproven concerns that it increased the risk of birth defects (72). Since that time, several investigations have shown the combination of doxylamine/pyridoxine to be both effective and safe, and in 2013, the US Food and Drug Administration approved this same formulation for the treatment of nausea and vomiting in pregnancy (reviewed in 73 and 74). The American and Canadian Colleges of Obstetrics and Gynecology and the Association of Professors of Gynecology and Obstetrics recommend the combination of doxylamine/pyridoxine as first-line therapy for nausea and vomiting during pregnancy (reviewed in 75).

The tolerable upper intake level (UL) for vitamin B_6 during pregnancy is 80 to 100 mg/day; see **Table 2**.

Vitamin B_{12}

In humans, vitamin B_{12} is needed as a cofactor for two enzymes. One converts homocysteine to the amino acid, methionine. Methionine is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions (76). DNA methylation that occurs during embryonic and fetal development modulates gene expression, cell differentiation, and the formation of organs (77). Thus, adequate vitamin B_{12} status during pregnancy is critical.

Inadequate dietary intake of vitamin B_{12} causes elevated homocysteine concentrations, which have been associated with adverse pregnancy outcomes, including preeclampsia, premature delivery, low placental weight, low birth weight, very low birth weight (<1,500 grams), small for gestational age, neural tube defects (NTDs), and stillbirth (48-50). Moreover, low serum concentrations of vitamin B_{12} during pregnancy have been linked to an increased risk for NTDs (78), and there is concern that folic acid supplementation during pregnancy may mask the clinical diagnosis of vitamin B_{12} deficiency. For these reasons, adequate vitamin B_{12} intake during pregnancy (RDA=2.6 µg/day) is important.

To ensure a daily intake of 6 to 30 µg of vitamin B_{12} in a form that is easily absorbed, the Linus Pauling Institute recommends that women who are planning a pregnancy take a daily multivitamin supplement or eat a breakfast cereal fortified with vitamin B_{12} (for more information, see the article on Vitamin B_{12}).

Vitamin C and Vitamin E

Because oxidative stress has been implicated in the pathogenesis of preeclampsia (79), nutritional status of the two antioxidant vitamins, vitamin C and vitamin E, may be important in preventing the condition. These vitamins have other biological functions; for more information, see the separate articles on Vitamin C and Vitamin E. Several trials have investigated whether supplementation with vitamins C and E improves pregnancy-associated hypertension or preeclampsia, but evidence supporting such an effect is largely lacking. An early placebo-controlled trial found that supplementation with 1,000 mg/day of vitamin C and 400 mg of vitamin E (*RRR*-α-tocopherol) was associated with a 61% reduction in the incidence of preeclampsia in women at increased risk for the condition (80). However, more recent randomized controlled trials have not found supplementation at these dosages to be effective in preventing preeclampsia in high- or low-risk women (81-84). Nevertheless, adequate intake of antioxidant vitamins is important throughout pregnancy. According to data from the US National Health and Nutrition Examination Survey (NHANES), 42%-46% and 85%-94% of US adults do not meet the estimated average requirement (EAR) for vitamin C and vitamin E, respectively (85). The Linus Pauling Institute's recommends that adults, including pregnant women, reach daily intakes of at least 400 mg of vitamin C and 15 mg (22.5 IU) of vitamin E.

Vitamin D

In 2010, the FNB of the Institute of Medicine set the RDA for vitamin D at 15 µg (600 IU)/day for all pregnant women (86). The FNB based this recommendation on a limited number of studies using bone health as the only indicator, assuming minimal sun exposure. Vitamin D, however, has a number of other roles in disease prevention and health (see the article on Vitamin D), and several vitamin D researchers believe that vitamin D requirements for adults, including pregnant women, are higher than the current RDA (87-91). Moreover, a number of studies indicate that vitamin D deficiency and insufficiency are quite common among pregnant women (92-101).

Low vitamin D status in pregnancy has been associated with an increased risk of adverse outcomes for both the mother and the infant. For pregnant women, vitamin D deficiency (serum 25-hydroxyvitamin D less than 50 nmol/L [20 ng/mL]) has been associated with an increased risk of preeclampsia and gestational diabetes (102, 103). For infants, low maternal vitamin D status has been associated with an increased risk of preterm birth (birth before 37 weeks of gestation) and low birth weight (a newborn weighing less than 2,500 grams) (104-106). A pooled analysis of 15 randomized controlled trials concluded that vitamin D supplementation raises serum 25-hydroxyvitamin D during pregnancy and may reduce the risk of preeclampsia, low birth weight, and preterm birth; notably, combined supplementation of vitamin D and calcium may increase the risk of preterm birth (107).

Vitamin D is found in very few foods, and prenatal supplements often contain only 10 µg (400 IU) of vitamin D. Sunlight exposure is the main source of the vitamin: vitamin D_3 (cholecalciferol) is synthesized in skin cells following exposure to ultraviolet-B radiation. However, the contribution of sun exposure to vitamin D status depends on many factors, including latitude, skin color, amount of skin exposed, duration of exposure, and the use of sunscreens, which effectively block skin production of vitamin D. Thus, vitamin D supplementation throughout pregnancy is likely needed to achieve body concentrations thought to benefit fetal and maternal health. The Linus Pauling Institute recommends that generally healthy adults, including pregnant women, take 2,000 IU (50 µg) of supplemental vitamin D daily. Because sun exposure, diet, skin color, and obesity have variable, substantial impact on body vitamin D concentrations, measuring serum concentrations of 25-hydroxyvitamin D — the clinical indicator of vitamin D status — is important. The Linus Pauling Institute recommends aiming for a serum 25-hydroxyvitamin D level of at least 75 nmol/L (30 ng/mL).

Vitamin K

The adequate intake (AI) for vitamin K (90 µg/day for women aged 19-50 years and 75 µg/day for those aged 14-18 years) is not increased during pregnancy, and a tolerable upper intake level (UL) has not been set for vitamin K. However, if taken during pregnancy, a number of drugs, including warfarin, rifampin, isoniazid, and anticonvulsants, may increase the risk of neonatal vitamin K deficiency and hemorrhagic disease of the newborn (108).

Placental transfer of vitamin K is low, thus all infants are born with low concentrations of vitamin K. A small proportion of newborns (0.25 to 1.1%) does not have enough vitamin K to make their blood clot and may develop vitamin K deficiency bleeding (VKDB) (109). There are three categories of VKDB depending on the age of onset: early (0-24 hours), classic (one to seven days), and late (two to 12 weeks) (110-112). Early VKDB is seen mainly in infants of mothers taking drugs that inhibit vitamin K, as listed above. Classic VKDB is more common and presents as bruising, gastrointestinal blood loss, or bleeding from the umbilicus, skin, or site of circumcision. Late VKDB is particularly concerning as it can lead to life-threatening intracranial bleeding. Randomized controlled trials have demonstrated that prophylactic intramuscular (IM) vitamin K injection of the newborn raises plasma vitamin K concentration, reduces PIVKA II (a marker of vitamin K deficiency), improves prothrombin time, and decreases the risk of classic VKDB compared to placebo (reviewed in 111). Administration of multiple oral doses of vitamin K can reduce PIVKA II concentrations and raise plasma vitamin K concentration but is associated with an increased incidence of late VKDB (109, 111, 113). The American Academy of Pediatrics and several international professional organizations recommend that all babies receive 0.5 to 1.0 mg intramuscular vitamin K_1 injection shortly after birth to prevent VKDB (109, 110, 114).

Minerals

Calcium

Although 200 to 250 mg/day of calcium is transferred to the fetus, primarily in the last trimester, dietary intake requirements of calcium are not increased due to maternal physiological adaptations. In particular, the efficiency of intestinal calcium absorption doubles during pregnancy, and the mineral can also be transiently mobilized from maternal stores (i.e., the skeleton) to support fetal needs for calcium. Permanent demineralization of bone during pregnancy has not been observed (86, 115). Moreover, there is no evidence from randomized controlled trials that calcium supplementation during pregnancy confers any benefit to maternal or fetal bone health (116, 117). The RDA is 1,300 mg/day for women aged 14-18 years and 1,000 mg/day for women aged 19-50 years.

Calcium intake during pregnancy, however, may influence the risk for pregnancy-induced hypertension (PIH). PIH, which occurs in 10% of pregnancies and is a major health risk for pregnant women and the fetus, is a term that includes gestational hypertension, preeclampsia, and eclampsia. Gestational hypertension is defined as an abnormally high blood pressure that usually develops after the 20th week of pregnancy. In addition to gestational hypertension, preeclampsia includes the development of edema (severe swelling) and proteinuria (protein in the urine). Preeclampsia may progress to eclampsia in which life-threatening convulsions and coma may occur (118). Risk factors for PIH include first pregnancies, multiple gestations (e.g., twins or triplets), chronic high blood pressure, diabetes, and some autoimmune diseases. Although the cause of PIH is not entirely understood, calcium metabolism appears to play a role. Low calcium intake during pregnancy may: (1) stimulate parathyroid hormone release, thereby increasing intracellular calcium and vascular smooth muscle contractility; and/or (2) stimulate renin release, leading to vasoconstriction and retention of sodium and fluid (119). Data from observational studies suggest an inverse relationship between dietary calcium intake and the incidence of PIH (120). Additionally, a recent systematic review of randomized, placebo-controlled trials (RCTs) reported that calcium supplementation during pregnancy (≥1,000 mg/day) was associated with a 35% lower risk of high blood pressure and a 55% lower risk of preeclampsia; the risk reduction for preeclampsia was even stronger for women considered to be at high risk for the condition (78% lower risk compared to placebo) and women with low dietary intake of calcium (64% lower risk compared to placebo) (121). This analysis also found that calcium supplementation lowered the risk of preterm birth by 24%, but no significant effect of calcium supplementation was found regarding the risk of stillbirth, admission to neonatal intensive care unit, or neonatal mortality before hospital discharge. Of four RCTs that monitored maternal death or serious morbidity, one RCT (122) reported a 20% reduced risk for the "severe maternal morbidity and mortality index" (a summary indicator defined as the presence of at least one of the following outcomes: maternal admission to intensive care or any special care unit, eclampsia, severe preeclampsia, placental abruption, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count], renal failure, or death) with calcium supplementation; no events occurred in the other three RCTs (121).

Chromium

Chromium is known to enhance the action of insulin; therefore, several studies have investigated the utility of chromium supplementation for the control of blood glucose concentrations in type 2 diabetes (see the article on Chromium). However, its use in gestational diabetes — a condition that affects 4.6%-9.2% of all pregnancies in the US (123) — has not been well studied. Gestational diabetes is a glucose intolerance that usually appears in the second or third trimester of pregnancy; blood glucose concentrations must be tightly controlled to prevent adverse effects on the developing fetus and other pregnancy complications. After delivery, glucose tolerance generally reverts to normal, but women are at a heightened risk of developing type 2 diabetes (124). In fact, a recent systematic review and meta-analysis found that the risk of developing type 2 diabetes in women diagnosed with gestational diabetes is more than 7-fold higher than women not diagnosed with gestational diabetes (125). Gestational diabetes is also considered a risk factor for cardiovascular disease (124). Two observational studies found that serum concentrations of chromium in pregnant women were not associated with glucose intolerance or gestational diabetes (126, 127), although serum chromium concentrations may not necessarily reflect tissue chromium concentrations. An eight-week placebo-controlled trial in 24 women with gestational diabetes found that supplementation in the form of chromium picolinate (4 µg/day of chromium per kilogram of body weight) was associated with lower fasting blood glucose and insulin concentrations (128). However, it is important to note that insulin therapy was still required to normalize the severely elevated blood glucose concentrations. Thus, more research, especially from randomized controlled trials, is needed to determine whether chromium supplementation has any utility in the treatment of gestational diabetes.

Iodine

Iodine requirements are increased by more than 45% during pregnancy: the RDA for pregnant women is 220 µg/day compared to 150 µg/day for women who are not pregnant. Adequate intake of this mineral is needed for maternal thyroid hormone production, and thyroid hormone is needed for myelination of the central nervous system and is thus essential for normal fetal brain development (129). If iodine deficiency leads to inadequate production of thyroid hormone during pregnancy, irreversible brain damage in the fetus may occur (130). Severe maternal iodine deficiency has also been associated with increased incidence of miscarriage, stillbirth, and birth defects (131).

One of the most devastating effects of severe maternal iodine deficiency is congenital hypothyroidism (132). A severe form of congenital hypothyroidism may lead to a condition that is sometimes referred to as cretinism and result in irreversible mental retardation. Cretinism occurs in two forms, neurologic and myxedematous, although there is considerable overlap between them. The neurologic form is characterized by mental and physical retardation and deafness; it results from maternal iodine deficiency that affects the fetus before its own thyroid is functional. The myxedematous or hypothyroid form is characterized by short stature and mental retardation (133). Severe maternal iodine deficiency has also been linked to neurocognitive deficits in the offspring (134). In severely iodine-deficient pregnant women, iodine supplementation effectively reduces rates of cretinism, and improves offspring cognitive function and survival (reviewed in 135). The timing of iodine supplementation appears to be important: supplementation should be initiated prior to conception and early in pregnancy (before the 10th week of gestation) in order to see beneficial effects on offspring neurocognitive outcomes (135).

Even mild forms of maternal iodine deficiency may have adverse effects on cognitive development in the offspring (136), though this outcome is less well studied. Randomized controlled trials conducted in moderately iodine deficient pregnant women demonstrate that iodine supplementation increases thyroid gland volume but has no effect on thyroid hormone concentrations compared to placebo (reviewed in 130 and 135). The extent to which supplementation in moderately iodine deficient pregnant women affects neurocognitive outcomes in their offspring is currently under investigation (137).

Iodine deficiency is now accepted as the most common cause of preventable brain damage in the world (131). Thus, adequate intake of the mineral throughout pregnancy is critical. A daily supplement providing 150 µg of iodine, as recommended by the American Thyroid Association (138), will help to ensure that US pregnant women consume sufficient iodine. However, it is important to note that several prenatal supplements and some multivitamin/mineral supplements on the market in the US do not contain iodine (139), presumably because manufacturers assume that women receive sufficient iodine through iodized salt and other food sources. For more information on iodine and iodine deficiency disorders, see the article on Iodine.

Iron

Iron requirements are significantly increased during pregnancy: the RDA is 27 mg/day for pregnant women of all ages compared to 15 to 18 mg/day for nonpregnant women. Many women have dietary iron intakes below current recommendations. National surveys in the US indicate that the average dietary iron intake is about 12 mg/day in nonpregnant women and 15 mg/day in pregnant women (140). Iron is needed for a number of biological functions (see the article on Iron), but during pregnancy, the mineral is generally needed to support growth and development of the fetus and placenta and to meet the increased demand for red blood cells to transport oxygen. Intestinal absorption of dietary iron increases during the second and third trimesters to accommodate for expansion of red cell mass (140). Maternal blood volume expands by almost 50% during pregnancy, which results in a hemodilution of red blood cells (141).

Despite maternal physiologic changes that enhance iron absorption, many women develop iron-deficiency or iron-deficiency anemia during pregnancy. The World Health Organization estimates that the worldwide prevalence of anemia among pregnant women is 42%; the prevalence of anemia is much higher in less developed nations compared with industrialized nations, with almost 90% of these anemic women living in Africa or Asia (142). In pregnant women in the US, the prevalence of iron deficiency is 18%, and the prevalence of iron-deficiency anemia is 5% (143). Anemias can be caused by deficiencies in other micronutrients, such as folate or vitamin B_{12}, but iron deficiency is the primary cause of anemia during pregnancy (1). Severe iron-deficiency anemia has been associated with an increased risk of maternal death (142) and with an increased risk of low birth weight infants (<2,500 grams), premature delivery, and perinatal mortality (144).

Two 2015 systematic reviews evaluated the effect of routine iron supplementation compared to placebo or no treatment on maternal and birth outcomes (145, 146). Both reviews found that routine supplementation with iron improved maternal iron status and decreased the risk of iron deficiency and iron-deficiency anemia at term. There is some indication that maternal iron supplementation could improve birth outcomes (namely preterm birth and low birth weight) in developing countries, but the evidence was deemed of low quality (146). Women taking higher doses of iron (≥60 mg/day) tended to have abnormally high hemoglobin values at term and were more likely to report side effects (146); side effects of high-dose iron supplements include nausea, constipation, vomiting, and diarrhea.

Iron status of the woman at the time of conception is important for a healthy pregnancy, to avoid postpartum anemia, and to provide the breast-feeding infant with sufficient iron stores until six months of age, when complementary feeding is recommended. Because of the increased demands for the mineral during the second and third trimesters of pregnancy, iron supplementation (30 mg/day) is usually recommended beginning at 12 weeks' gestation (147). Absorption of nonheme iron, which is the form of iron found in supplements, is affected by a number of enhancers (e.g., vitamin C) as well as inhibitors (e.g., polyphenols found in tea and coffee). In general, iron supplements are better absorbed on an empty stomach. High doses of iron supplements taken together with zinc supplements on an empty stomach can inhibit the absorption of zinc (140, 148); supplemental iron at 38 to 65 mg/day of elemental iron may decrease zinc absorption (149). For more information about dietary and supplemental sources of iron, as well as the side effects and safety of iron, see the article on Iron.

Magnesium

The mineral magnesium plays a number of important roles in the structure and the function of the human body (see the article on Magnesium), and adequate intake of the mineral is needed for normal embryonic and fetal development. National dietary surveys indicate that magnesium insufficiency is relatively common in the US, with 56% of American adults not meeting the EAR — the nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a particular life stage and gender group (150). Good sources of magnesium include green leafy vegetables, whole grains, and nuts (see the article on Magnesium). Several multivitamin/mineral and prenatal supplements do not contain magnesium or contain no more than 100 mg of magnesium.

Preeclampsia-eclampsia is a disease that is unique to pregnancy and may occur anytime after 20 weeks' gestation. Preeclampsia is defined as the presence of elevated blood pressure and protein in the urine; severe swelling (edema) may also be present. Eclampsia occurs with the addition of seizures to these symptoms. Approximately 5%-8% of women with preeclampsia go on to develop eclampsia in developing countries, which is a significant cause of maternal death (84).

A 2014 pooled analysis of randomized controlled trials concluded that oral magnesium supplementation during pregnancy has no significant effect on perinatal mortality, small-for-gestational age, or the risk of preeclampsia (151). Intravenous administration of high-dose magnesium sulfate has been the treatment of choice for preventing eclamptic seizures that may occur in association with preeclampsia-eclampsia in late pregnancy or during labor (152-154). Magnesium is believed to relieve cerebral blood vessel spasm and promote peripheral vasodilation, thereby increasing blood flow to the brain (155-157).

Zinc

The RDA for zinc is increased during pregnancy (from 8 mg/day-9 mg/day to 11 mg/day-12 mg/day), and pregnant women, especially teenagers, are at increased risk of zinc deficiency. It has been estimated that 82% of pregnant women in the world may have inadequate intake of dietary zinc (158), leading to poor nutritional status of the mineral. Poor nutritional status of zinc during pregnancy has been associated with a number of adverse outcomes, including low birth weight (<2,500 grams), premature delivery, labor and delivery complications, and congenital anomalies (159). However, the results of maternal zinc supplementation trials in the US and developing countries have been mixed (160). A 2014 systematic review of 16 randomized controlled trials found that zinc supplementation during pregnancy was associated with a 14% reduction in premature deliveries; the lower incidence of preterm births was observed mainly in low-income women (161). This analysis, however, did not find zinc supplementation to benefit other indicators of maternal or infant health.

It is important to note that supplemental levels of iron (38 to 65 mg/day of elemental iron), but not dietary levels of iron, may decrease zinc absorption (149). Because iron supplementation is often recommended during pregnancy (see Iron above), pregnant women who take more than 60 mg/day of elemental iron may want to take a prenatal or multivitamin-mineral supplement that also includes zinc (162).

Other Nutrients

Choline

Choline can be synthesized by the body in small amounts, but dietary intake is needed to maintain health (163). Choline is essential for embryonic and fetal brain development, liver function, and placental function (164). The choline metabolite betaine is a source of methyl (CH_3) groups required for methylation reactions; DNA methylation that occurs during embryonic and fetal development modulates gene expression, cell differentiation, and the formation of organs (77). A mother delivers large amounts of choline to the fetus across the placenta and to the infant via breast milk, placing an increased demand on maternal stores of choline during pregnancy and lactation (164). The induction of *de novo* choline synthesis by the high levels of estrogen during pregnancy helps to meet this increased demand (165). Additionally, pregnant women are encouraged to consume choline-rich foods, such as eggs, meat, and seafood (for dietary sources, see the article on Choline). The adequate intake (AI) for pregnant women is 450 mg/day of choline, slightly higher than the 425 mg/day recommended for nonpregnant women (166).

Case-control studies have reported mixed results regarding the relationship between dietary choline intake or blood choline concentration and the risk of neural tube defects (NTDs). One case-control study reported a lower risk of having an NTD-affected pregnancy in those with the highest intake of betaine and choline combined (167), while two other studies found no association between maternal choline intake and NTD risk (168, 169). Similarly, one case-control study found low serum choline concentration was associated with a higher risk of NTDs (170), while another study found no such association (171). Additionally, it is not known if supplementation with choline or betaine, like supplementation with folic acid (see Folate above), will lower the incidence of NTDs. More research is needed to determine whether choline is involved in the etiology of NTDs.

Maternal intake of choline during pregnancy could possibly affect cognitive abilities of the offspring. Choline supplementation in pregnant rats, as well as rat pups during the first month of life, leads to improved performance in spatial memory tests months after choline supplementation has been discontinued (172). A review by McCann et al. discusses the experimental evidence from rodent studies regarding the availability of choline during prenatal development and cognitive function in the offspring (173). It is not clear whether findings in rodent studies are applicable to humans. One randomized controlled trial demonstrated that choline supplementation (750 mg/day of choline in the form of phosphatidylcholine administered from week 18 of gestation through 90 days postpartum) in pregnant women consuming a moderate-choline diet (approximately 360 mg/day) was safe but did not enhance infant cognitive function at 10 or 12 months of age (174).

Finally, choline is important for homocysteine metabolism during pregnancy. Methyl groups derived from choline may be used to convert homocysteine to methionine. Elevated blood homocysteine concentrations have been associated with increased risk of preeclampsia, premature delivery, low placental weight, low birth weight (<2,500 grams), very low birth weight (<1,500 grams), small for gestational age, NTDs, and stillbirth (48-50).

Essential fatty acids

Although not micronutrients, certain fatty acids are required in the maternal diet during pregnancy and lactation; the US Institute of Medicine's adequate intake (AI) recommendations for omega-3 and omega-6 fatty acids during pregnancy and lactation are listed in the separate article on Essential Fatty Acids. For more information on the importance of omega-3 fatty acids during these life stages, see two sections in the separate article on essential fatty acids: Visual and neurological development and Pregnancy and lactation. Information about environmental contaminants in fish and supplements is included in the sections, Contaminants in fish and Contaminants in supplements.

Safety in Pregnancy

Table 2. UL for Micronutrients During Pregnancy

Micronutrient	Age	UL
Biotin	14-50 years	ND[a]
Folate	14-18 years	800 μg/day[b]
	19-50 years	1,000 μg/day[b]
Niacin	14-18 years	30 mg/day[b]
	19-50 years	35 mg/day[b]
Pantothenic Acid	14-50 years	ND
Riboflavin	14-50 years	ND
Thiamin	14-50 years	ND
Vitamin A	14-18 years	2,800 μg (9,333 IU)/day[c]
	19-50 years	3,000 μg (10,000 IU)/day[c]
Vitamin B_6	14-18 years	80 mg/day
Vitamin B_6	19-50 years	100 mg/day
Vitamin B_{12}	14-50 years	ND
Vitamin C	14-18 years	1,800 mg/day
	19-50 years	2,000 mg/day
Vitamin D	14-50 years	100 μg (4,000 IU)/day
Vitamin E	14-18 years	800 mg (1,200 IU)/day[d]
	19-50 years	1,000 mg (1,500 IU)/day[d]
Vitamin K	14-50 years	ND
Calcium	14-18 years	3,000 mg/day
	19-50 years	2,500 mg/day
Chromium	14-50 years	ND
Copper	14-18 years	8 mg/day
	19-50 years	10 mg/day
Fluoride	14-50 years	10 mg/day
Iodine	14-18 years	900 μg/day
	19-50 years	1,100 μg/day
Iron	14-50 years	45 mg/day
Magnesium	14-50 years	350 mg/day[e]
Manganese	14-18 years	9 mg/day
	19-50 years	11 mg/day
Molybdenum	14-18 years	1,700 μg/day
	19-50 years	2,000 μg/day
Phosphorus	14-50 years	3,500 mg/day
Potassium	14-50 years	ND
Selenium	14-50 years	400 μg/day
Sodium	14-50 years	ND
Zinc	14-18 years	34 mg/day
	19-50 years	40 mg/day
Choline[f]	14-18 years	3,000 mg/day
	19-50 years	3,500 mg/day

[a] ND, not determinable because data are lacking
[b] Applies to the synthetic form in fortified foods and supplements
[c] Applies to only preformed vitamin A (retinol)
[d] Applies to any form of supplemental α-tocopherol
[e] Applies only to the supplemental form
[f] Considered an essential nutrient, although not strictly a micronutrient

Maternal Micronutrient Requirements During Lactation

Breast-feeding confers health benefits to the child, as well as the mother (175). Breast milk is the ideal source of nutrition for the infant and also contains a number of bioactive compounds important in immunity, such as antibodies, cytokines, antimicrobial agents, and oligosaccharides (176). The American Academy of Pediatrics recommends exclusive breast-feeding for the first six months of infancy, followed by continued breast-feeding as complementary foods are introduced, with continuation of breast-feeding until 12 months postpartum or longer as mutually desired by the mother and child (177). The World Health Organization recommends exclusive breast-feeding for the first six months of life and continued breast-feeding, with complementary feeding, up to two years or more postpartum (178). There are, however, a few exceptions when breast-feeding is contraindicated, including those listed on the CDC website.

Lactation is extremely energy expensive (exceeding pre-pregnancy demands by approximately 500 kcal/day), and macronutrient requirements for breast-feeding women are even higher than during pregnancy (175). Likewise, the intake recommendations (RDA or AI) for most micronutrients, which are based on amounts secreted in breast milk, are higher for lactating women compared to pregnant women (see **Table 3**). One notable exception is the RDA for iron, which is significantly lower during lactation (9 to 10 mg/day) compared to pregnancy (27 mg/day) (140). Breast milk is considered to be low in iron; however, the iron content of breast milk is not influenced by changes in maternal iron status, such as through maternal supplementation (59). The RDA for folate is also lower during lactation compared with pregnancy. Dietary intake recommendations for calcium remain unchanged for lactating women compared to recommendations for nonlactating women, and calcium content in breast milk does not reflect maternal intake of the mineral. Adequate calcium is maintained in breast milk because of maternal physiological changes that involve transient bone resorption; increased maternal intake of calcium through diet and supplementation does not prevent maternal bone demineralization, and studies have shown that maternal bone mineral content is restored upon weaning (179).

In general, the amounts of water-soluble vitamins (B vitamins and vitamin C) in breast milk reflect maternal intake from diet and/or supplements. Thus, meeting daily intake recommendations for these micronutrients is important for the health of the child. Maternal vitamin deficiencies can negatively affect infant growth and development; for instance, vitamin B_{12} deficiency during infancy can impair brain development and cause neurological problems (180). Vitamin B_{12} deficiency has been documented in nursing infants of mothers who have untreated pernicious anemia and also in women who are strict vegetarians (vegans) (181). Vitamin B_{12} is found only in foods of animal origin and fortified foods, and lactating women who follow vegetarian diets should take supplemental vitamin B_{12}. Vitamin B_{12} deficiency that results from pernicious anemia can easily be corrected with high-dose daily supplementation or with monthly intramuscular injections of the vitamin (see the article on Vitamin B_{12}). However, there has been relatively little research on the effect of oral vitamin B_{12} supplementation in lactating women, and it has been suggested that supplementation during lactation may be too late to restore adequate milk concentrations and infant status (182). Supplementation during pregnancy may more effectively improve infant vitamin B_{12} status. For instance, oral daily vitamin B_{12} supplementation (50 μg/day) administered from <14 weeks gestation through 6 weeks postpartum significantly increased maternal plasma and breast milk concentrations of vitamin B_{12} and improved infant vitamin B_{12} status (183). The concentrations of other water-soluble vitamins in breast milk, including thiamin, riboflavin, and vitamin B_6, are also strongly dependent on maternal intake of these vitamins (59, 182). Likewise, vitamin C concentration in human milk varies with the vitamin C status of the mother. Vitamin C supplementation can moderately increase concentrations of the vitamin in breast milk, especially in lactating women with poor vitamin C status (184), and maternal intakes of 100 mg/day maximize the amount of vitamin C in breast milk (185).

Compared to water-soluble vitamins, the concentrations of fat-soluble vitamins (vitamins A, D, E, and K) in breast milk are less correlated with maternal dietary intake. The RDA for vitamin A during lactation is 1,200 to 1,300 μg/day (4,000 to 4,333 IU/day). At such levels of maternal intake, breast milk is a good source of vitamin A and provides the infant with a sufficient amount of the vitamin (186). In contrast, breast milk is considered to be low in vitamins D and K. Vitamin D concentrations in human milk are dependent on maternal vitamin D status, which is determined by the woman's sun exposure and dietary and supplemental intake. Vitamin D concentrations are low in breast milk, presumably because many women have insufficient vitamin D status. Vitamin D supplementation during lactation has been shown to improve vitamin D status in the woman and the infant (187). The RDA for lactating women is 600 IU/day of vitamin D, but intake at this level in the absence of sun exposure likely results in insufficient amounts for the infant. To prevent vitamin D deficiency and rickets in infants, the American Academy of Pediatrics recommends that all breast-fed and partially breast-fed infants be given a vitamin D supplement of 400 IU/day (177). Liquid vitamin D supplements are commercially available for infant supplementation. The Linus Pauling Institute recommends that all adults take 2,000 IU/day of supplemental vitamin D and aim for a serum 25-hydroxyvitamin D level of at least 75 nmol/L (30 ng/mL). Human milk is also relatively low in vitamin K. Thus, exclusively breast-fed newborns are at increased risk for vitamin K deficiency. In general, newborns have low vitamin K status for the following reasons: (1) vitamin K is not easily transported across the placental barrier; (2) the newborn's intestines are not yet colonized with bacteria that synthesize vitamin K; and (3) the vitamin K cycle may not be fully functional in newborns, especially premature infants (188). Vitamin K deficiency in newborns may result in a bleeding disorder called vitamin K deficiency bleeding (VKDB). Because VKDB is life-threatening and easily prevented, the American Academy of Pediatrics and a number of similar international organizations recommend that an injection of phylloquinone (vitamin K_1) be administered to all newborns shortly after birth (110, 114, 177). Additionally, the vitamin E content in breast milk varies with maternal diet and vitamin E supplement use (184, 186). The RDA for vitamin E during lactation is 19 mg/day (28.5 IU/day) of α-tocopherol. National surveys indicate that more than 90% of US adults have daily vitamin E intakes below 12 mg (18 IU) (85).

Maternal dietary intake recommendations for the 14 essential minerals during lactation are shown in **Table 3**. The content of minerals in breast milk does not correlate well with maternal intake or status, except for iodine and selenium (1, 176). Iodine requirements are increased during lactation: breast-feeding women require 290 μg/day of iodine compared to 220 μg/day for pregnant women and 150 μg/day for nonpregnant, nonlactating women (129). Iodine-deficient women who are breast-feeding may not be able to provide sufficient iodine to their infants who are particularly vulnerable to the effects of iodine deficiency (see the article on Iodine). A daily supplement providing 150 μg of iodine, as recommended by the American Thyroid Association (138), will help to ensure that US breast-feeding women consume sufficient iodine during these critical periods. Additionally, the RDA for selenium is slightly higher for lactating women (from 60 to 70 μg/day), and selenium content in breast milk reflects maternal intake (189).

Table 3. RDA for Maternal Micronutrients During Lactation

Micronutrient	Age	RDA
Biotin	14-50 years	35 μg/day (AI)
Folate	14-50 years	500 μg/day[a]
Niacin	14-50 years	17 mg/day[b]
Pantothenic Acid	14-50 years	7 mg/day (AI)
Riboflavin	14-50 years	1.6 mg/day
Thiamin	14-50 years	1.4 mg/day
Vitamin A	14-18 years	1,200 μg (4,000 IU)/day[c]
	19-50 years	1,300 μg (4,333 IU)/day[c]
Vitamin B_6	14-50 years	2.0 mg/day
Vitamin B_{12}	14-50 years	2.8 μg/day
Vitamin C	14-18 years	115 mg/day
	19-50 years	120 mg/day
Vitamin D	14-50 years	15 μg (600 IU)/day
Vitamin E	14-50 years	19 mg (28.5 IU)/day[d]
Vitamin K	14-18 years	75 μg/day (AI)
	19-50 years	90 μg/day (AI)
Calcium	14-18 years	1,300 mg/day
	19-50 years	1,000 mg/day
Chromium	14-18 years	44 μg/day (AI)
	19-50 years	45 μg/day (AI)
Copper	14-50 years	1.3 mg/day
Fluoride	14-50 years	3 mg/day (AI)
Iodine	14-50 years	290 μg/day
Iron	14-18 years	10 mg/day
	19-50 years	9 mg/day
Magnesium	14-18 years	360 mg/day
	19-30 years	310 mg/day
	31-50 years	320 mg/day
Manganese	14-50 years	2.6 mg/day (AI)
Molybdenum	14-50 years	50 μg/day
Phosphorus	14-18 years	1,250 mg/day
	19-50 years	700 mg/day
Potassium	14-18 years	2,500 mg/day (AI)
	19-50 years	2,800 mg/day (AI)
Selenium	14-50 years	70 μg/day
Sodium	14-50 years	1,500 mg/day (AI)
Zinc	14-18 years	13 mg/day
	19-50 years	12 mg/day
Choline[e]	14-50 years	550 mg/day (AI)

AI, adequate intake
[a] Dietary Folate Equivalents
[b] NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin
[c] Retinol Activity Equivalents
[d] α-Tocopherol
[e] Considered an essential nutrient, although not strictly a micronutrient

Safety in Lactation

The tolerable upper intake level (UL) for each micronutrient is shown in the **Table 4**. The UL, established by the Food and Nutrition Board of the Institute of Medicine, is the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals.

Table 4. UL for Maternal Micronutrients During Lactation

Micronutrient	Age	UL
Biotin	14-50 years	ND[a]
Folate	14-18 years	800 μg/day[b]
	19-50 years	1,000 μg/day[b]
Niacin	14-18 years	30 mg/day[b]
	19-50 years	35 mg/day[b]
Pantothenic Acid	14-50 years	ND
Riboflavin	14-50 years	ND
Thiamin	14-50 years	ND
Vitamin A	14-18 years	2,800 μg (9,333 IU)/day[c]
	19-50 years	3,000 μg (10,000 IU)/day[c]
Vitamin B_6	14-18 years	80 mg/day
Vitamin B_6	19-50 years	100 mg/day
Vitamin B_{12}	14-50 years	ND
Vitamin C	14-18 years	1,800 mg/day
	19-50 years	2,000 mg/day
Vitamin D	14-50 years	100 μg (4,000 IU)/day
Vitamin E	14-18 years	800 mg (1,200 IU)/day[d]
	19-50 years	1,000 mg (1,500 IU)/day[d]
Vitamin K	14-50 years	ND
Calcium	14-18 years	3,000 mg/day
	19-50 years	2,500 mg/day
Chromium	14-50 years	ND
Copper	14-18 years	8 mg/day
	19-50 years	10 mg/day
Fluoride	14-50 years	10 mg/day
Iodine	14-18 years	900 μg/day
	19-50 years	1,100 μg/day
Iron	14-50 years	45 mg/day
Magnesium	14-50 years	350 mg/day[e]
Manganese	14-18 years	9 mg/day
	19-50 years	11 mg/day
Molybdenum	14-18 years	1,700 μg/day
	19-50 years	2,000 μg/day
Phosphorus	14-50 years	4,000 mg/day
Potassium	14-50 years	ND
Selenium	14-50 years	400 μg/day
Sodium	14-50 years	ND
Zinc	14-18 years	34 mg/day
	19-50 years	40 mg/day
Choline[f]	14-18 years	3,000 mg/day
	19-50 years	3,500 mg/day

[a] ND, not determinable because data are lacking
[b] Applies to the synthetic form in fortified foods and supplements
[c] Applies to only preformed vitamin A (retinol)
[d] Applies to any form of supplemental α-tocopherol
[e] Applies only to the supplemental form
[f] Considered an essential nutrient, although not strictly a micronutrient

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Older Adults

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Micronutrients for Older Adults

Introduction

Listed below are vitamin and mineral dietary intake recommendations for individuals over the age of 50 years. For each micronutrient, the Food and Nutrition Board of the Institute of Medicine establishes a recommended dietary allowance (RDA) or adequate intake (AI). Generally, the Linus Pauling Institute supports the recommendations of the Food and Nutrition Board, but any discrepancies in dietary recommendations are listed in the rightmost column of the table. Additionally, more information on the Linus Pauling Institute recommendation for a specific micronutrient can be found by clicking on the name of the micronutrient of interest.

Table 1. Micronutrient Requirements for Older Adults (>50 years)

	Food and Nutrition Board Recommendations (RDA except where otherwise noted)		Linus Pauling Institute Recommendation
Micronutrient	**Men**	**Women**	
Vitamins			
Biotin	30 µg/day (AI)	30 µg/day (AI)	
Folate	400 µg/day	400 µg/day	
Niacin	16 mg NE*/day	14 mg NE/day	
Pantothenic acid	5 mg/day (AI)	5 mg/day (AI)	
Riboflavin	1.3 mg/day	1.1 mg/day	
Thiamin	1.2 mg/day	1.1 mg/day	
Vitamin A	900 µg (3,000 IU)/day	700 µg (2,333 IU)/day	
Vitamin B_6	1.7 mg/day	1.5 mg/day	2.0 mg/day
Vitamin B_{12}	2.4 µg/day#	2.4 µg/day#	100-400 µg/day of crystalline vitamin B_{12}
Vitamin C	90 mg/day	75 mg/day	≥400 mg/day
Vitamin D (51-70 years)	15 µg (600 IU)/day	15 µg (600 IU)/day	2,000 IU/day from supplements
Vitamin D (>70 years)	20 µg (800 IU)/day	20 µg (800 IU)/day	2,000 IU/day from supplements
Vitamin E	15 mg (22.5 IU)/day	15 mg (22.5 IU)/day	
Vitamin K	120 µg/day (AI)	90 µg/day (AI)	
Minerals			
Calcium (51-70 years)	1,000 mg/day	1,200 mg/day	
Calcium (>70 years)	1,200 mg/day	1,200 mg/day	
Chromium	30 µg/day (AI)	20 µg/day (AI)	
Copper	900 µg/day	900 µg/day	
Fluoride	4 mg/day (AI)	3 mg/day (AI)	
Iodine	150 µg/day	150 µg/day	
Iron	8 mg/day	8 mg/day	No supplement
Magnesium	420 mg/day	320 mg/day	No supplement providing >350 mg/day
Manganese	2.3 mg/day (AI)	1.8 mg/day (AI)	
Molybdenum	45 µg/day	45 µg/day	
Phosphorus	700 mg/day	700 mg/day	
Potassium	3.4 g/day (AI)	2.6 g/day (AI)	
Selenium	55 µg/day	55 µg/day	
Sodium	1.5 g/day (AI)	1.5 g/day (AI)	
Zinc	11 mg/day	8 mg/day	

*NE, niacin equivalent: 1 mg NE = 60 mg of tryptophan = 1 mg niacin
#Vitamin B_{12} intake should be from supplements or fortified foods due to the age-related increase in malabsorption
Abbreviations: µg=microgram; mg=milligram; g=gram; IU=International Unit; RDA=Recommended Dietary Allowance; AI=Adequate Intake

Linus Pauling Institute Recommendations

Vitamins

Biotin

Presently, there is no indication that older adults have an increased requirement for biotin. If dietary biotin intake is not sufficient, a daily multivitamin/mineral supplement will generally provide an intake of at least 30 µg/day of biotin.

Folate

The Linus Pauling Institute recommends that adults take a 400 µg supplement of folic acid daily, in addition to folate and folic acid consumed in the diet. A daily multivitamin/mineral supplement, containing 100% of the Daily Value (DV) for folic acid provides 400 µg of folic acid. Even with a larger than average intake of folic acid from fortified food, it is unlikely that an individual's daily folic acid intake would regularly exceed the tolerable upper intake level (UL) of 1,000 µg/day established by the Food and Nutrition Board. The recommendation for 400 µg/day of supplemental folic acid as part of a daily multivitamin/mineral supplement, in addition to a folate-rich diet, is especially important for older adults because blood homocysteine levels tend to increase with age.

Niacin

Dietary surveys indicate that 15% to 25% of older adults do not consume enough niacin in their diets to meet the RDA (16 mg NE/day for men and 14 mg NE/day for women), and that dietary intake of niacin decreases between the ages of 60 and 90 years. Thus, it is advisable for older adults to supplement their dietary intake with a multivitamin/mineral supplement, which will generally provide at least 20 mg of niacin daily.

Pantothenic acid

Presently, there is little evidence that older adults differ in their intake or requirement for pantothenic acid. Most multivitamin/mineral supplements provide at least 5 mg/day of pantothenic acid. The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 5 mg/day of pantothenic acid for older adults. A varied diet should provide enough pantothenic acid for most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement, containing 100% of the Daily Value (DV), will ensure an intake of at least 5 mg/day of pantothenic acid.

Riboflavin

Some experts in nutrition and aging feel that the RDA of riboflavin (1.3 mg/day for men and 1.1 mg/day for women) leaves little margin for error in people over 50 years of age (1, 2). A study of independently living people between 65 and 90 years of age found that almost 25% consumed less than the recommended riboflavin intake, and 10% had biochemical evidence of deficiency (3). Epidemiological studies of cataract prevalence indicate that riboflavin intakes of 1.6 to 2.2 mg/day may reduce the risk of developing age-related cataracts. Additionally, older people suffering from acute ischemic stroke were found to be deficient for riboflavin (4), and riboflavin deficiency has been linked to a higher risk of fracture in postmenopausal women with the *MTHFR* 677T variant (5). Individuals whose diets may not supply adequate riboflavin, especially those over 50 years of age, should consider taking a multivitamin/mineral supplement, which generally provides at least 1.7 mg/day of riboflavin.

Thiamin

Presently, there is no evidence that the requirement for thiamin is increased in older adults, but some studies have found inadequate dietary intake and thiamin insufficiency to be more common in elderly populations (2). Thus, it would be prudent for older adults to take a multivitamin/mineral supplement, which will generally provide at least 1.5 mg of thiamin/day.

Vitamin A

Presently, there is little evidence that the requirement for vitamin A in older adults differs from that of younger adults. Additionally, vitamin A toxicity may occur at lower doses in older adults than in younger adults. Further, data from observational studies suggested an inverse association between intakes of preformed vitamin A in excess of 1,500 µg RAE (5,000 IU)/day and risk of hip fracture in older people (see the Safety section in the article on Vitamin A). Yet, following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement daily could supply as much as 5,000 IU/day of retinol, the amount that has been associated with adverse effects on bone health in older adults. For this reason, we recommend taking a multivitamin/mineral supplement that provides no more than 2,500 IU (750 µg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene. As for all age groups, high potency vitamin A supplements should not be used without medical supervision due to the risk of toxicity.

Vitamin B_6

Early metabolic studies have indicated that the requirement for vitamin B_6 in older adults is approximately 2 mg daily (6). Yet, the analysis of the US population survey (NHANES) 2003-2004 showed that adequate vitamin B_6 status and low homocysteine levels were associated with total vitamin B_6 intakes equal to and above 3 mg/day in people aged 65 years and older (7). The Linus Pauling Institute recommends that older adults take a multivitamin/mineral supplement, which provides at least 2.0 mg of vitamin B_6 daily.

Vitamin B_{12}

Because vitamin B_{12} malabsorption and vitamin B_{12} deficiency are more common in older adults, the Linus Pauling Institute recommends that adults older than 50 years take 100 to 400 µg/day of supplemental vitamin B_{12}.

Vitamin C

Although it is not yet known with certainty whether older adults have higher requirements for vitamin C, some older populations have been found to have vitamin C intakes considerably below the RDA of 75 and 90 mg/day for women and men, respectively. A vitamin C intake of at least 400 mg daily may be particularly important for older adults who are at higher risk for age-related chronic diseases. In addition, a meta-analysis of 36 publications examining the relationship between vitamin C intake and plasma concentrations of vitamin C concluded that older adults (aged 60-96 years) have considerably lower plasma levels of vitamin C following a certain intake of vitamin C compared with younger individuals (aged 15-65 years) (8), suggesting that older adults have higher vitamin C requirements. Pharmacokinetic studies in older adults have not yet been conducted, but evidence suggests that the efficiency of one of the molecular mechanisms for the cellular uptake of vitamin C declines with age (9). Because maximizing blood levels of vitamin C may be important in protection against oxidative damage to cells and biological molecules, a vitamin C intake of at least 400 mg daily is particularly important for older adults who are at higher risk for chronic diseases caused, in part, by oxidative damage, such as heart disease, stroke, certain cancers, and cataract.

Vitamin D

The Linus Pauling Institute recommends that generally healthy adults take 2,000 IU (50 µg) of supplemental vitamin D daily. Most multivitamins contain 400 IU of vitamin D, and single ingredient vitamin D supplements are available for additional supplementation. Sun exposure, diet, skin color, and obesity have variable, substantial impact on body vitamin D levels. To adjust for individual differences and ensure adequate body vitamin D status, the Linus Pauling Institute recommends aiming for a serum 25-hydroxyvitamin D level of at least 80 nmol/L (32 ng/mL). Numerous observational studies have found that serum 25-hydroxyvitamin D levels of 80 nmol/L (32 ng/mL) and above are associated with reduced risk of bone fractures, several cancers, multiple sclerosis, and type 1 (insulin-dependent) diabetes. Daily supplementation with 2,000 IU (50 µg) of vitamin D is especially important for older adults because aging is associated with a reduced capacity to synthesize vitamin D in the skin upon sun exposure.

Vitamin E

The RDA for adults of all ages is 15 mg (22.5 IU) per day of α-tocopherol. Notably, more than 90% of individuals aged two years and older in the US do not meet the daily requirement for vitamin E from food sources alone. Major sources of vitamin E in the American diet are vegetable oils, nuts, whole grains, and green leafy vegetables. LPI recommends that healthy older adults take a daily multivitamin/mineral supplement, which usually contains 30 IU of synthetic vitamin E, or 90% of the RDA.

Vitamin K

Older adults are at increased risk of osteoporosis and hip fracture. Because adequate intake of vitamin K is essential in maintaining bone health, the Linus Pauling Institute recommends that adults take a multivitamin/mineral supplement and consume at least one cup of dark green leafy vegetables daily. Although the AI for vitamin K was recently increased, it is not clear if it will be enough to optimize the γ-carboxylation of vitamin K-dependent proteins in bone (see the section on Osteoporosis in the article on vitamin K). Multivitamins generally contain 10 to 25 µg of vitamin K, whereas vitamin K or "bone" supplements may contain 100 to 120 µg of vitamin K. To consume the amount of vitamin K associated with a decreased risk of hip fracture in the Framingham Heart Study (about 250 µg/day) (10), an individual would need to eat a little more than ½ cup of chopped broccoli or a large salad of mixed greens every day. In addition to taking a multivitamin/mineral supplement and eating at least one cup of dark green leafy vegetables daily, replacing dietary saturated fat (e.g., butter and cheese) with monounsaturated fat (e.g., olive and canola oils) will increase dietary vitamin K intake and may also decrease the risk of cardiovascular disease.

Minerals

Calcium

To minimize bone loss, older men (>70 years) and postmenopausal women should consume a total (diet plus supplements) of 1,200 mg/day of calcium. Men aged 51-70 years should consume 1,000 mg of calcium per day. No multivitamin/mineral supplement contains the RDA for calcium (1,000-1,200 mg/day) because the resulting pill would be too large to swallow. If your total daily calcium intake doesn't add up to 1,000 mg, LPI recommends taking an extra calcium supplement with a meal.

Chromium

Although the requirement for chromium is not known to be higher for older adults, one study found that chromium concentrations in hair, sweat, and urine decreased with age (11). Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement containing 100% of the daily values (DV) of most nutrients should provide sufficient chromium for most older adults.

Because impaired glucose tolerance and type 2 diabetes are associated with potentially serious health problems, individuals considering high-dose chromium supplementation to treat either condition should do so in collaboration with a qualified health care provider.

Copper

Aging has not been associated with significant changes in the requirement for copper (12); thus, the Linus Pauling Institute recommendation for copper intake in older adults is the same as younger adults. The RDA for copper (900 µg/day for all adults) is sufficient to prevent deficiency, but the lack of clear indicators of copper nutritional status in humans makes it difficult to determine the level of copper intake most likely to promote optimum health or prevent chronic disease. A varied diet should provide enough copper for most people. For those who are concerned that their diet may not provide adequate copper, a multivitamin/mineral supplement will generally provide at least the RDA for copper.

Fluoride

The safety and public health benefits of optimally fluoridated water for prevention of tooth decay in people of all ages have been well established. The Linus Pauling Institute supports the recommendations of the American Dental Association and the Centers for Disease Control and Prevention, which include optimally fluoridated water and the use of fluoride toothpaste, fluoride mouth rinse, fluoride varnish, and when necessary, fluoride supplementation. Due to the risk of fluorosis, any fluoride supplementation should be prescribed and closely monitored by a dentist or physician.

Iodine

The RDA for iodine (150 µg/day for men and women) is sufficient to ensure normal thyroid function. There is presently no evidence that iodine intakes higher than the RDA are beneficial. Most people in the US consume more than sufficient iodine in their diets, making supplementation unnecessary.

Iron

A study in an elderly population found that high iron stores were much more common than iron deficiency (13). Thus, older adults should not generally take nutritional supplements containing iron unless they have been diagnosed with iron deficiency. Moreover, it is extremely important to determine the underlying cause of the iron deficiency, rather than simply treating it with iron supplements.

Magnesium

Older adults are less likely than younger adults to consume enough magnesium to meet their needs and should therefore take care to eat magnesium-rich food in addition to taking a multivitamin/mineral supplement daily. However, no multivitamin/mineral supplement contains 100% of the DV for magnesium. If you don't eat plenty of green leafy vegetables, whole grains, and nuts, you likely are not getting enough magnesium from your diet. Older adults are more likely to have impaired kidney function than younger individuals, they should avoid taking more than 350 mg/day of supplemental magnesium without medical consultation (see the section on Safety in the article on magnesium).

Manganese

The requirement for manganese is not known to be higher for older adults compared to younger adults. However, liver disease is more common in older adults and may increase the risk of manganese toxicity by decreasing the elimination of manganese from the body (see the section on Toxicity in the article on manganese). Manganese supplementation beyond 100% of the Daily Value (DV=2 mg/day) is not recommended.

Molybdenum

Because aging has not been associated with significant changes in the requirement for molybdenum (14), the Linus Pauling Institute recommendation for older adults is the same as that for younger adults. Specifically, the RDA for molybdenum, 45 µg/day for adults of all ages, is sufficient to prevent deficiency. Although the intake of molybdenum most likely to promote optimum health is not known, there is presently no evidence that intakes higher than the RDA are beneficial. Most people in the US consume more than sufficient molybdenum in their diets, making supplementation unnecessary. Following the Linus Pauling Institute's general recommendation to take a multivitamin/mineral supplement that contains 100% of the daily values (DV) for most nutrients is likely to provide 75 µg/day of molybdenum because the DV for molybdenum has not been revised to reflect the most recent RDA. Although the amount of molybdenum presently found in most multivitamin/mineral supplements is higher than the RDA, it is well below the tolerable upper intake level (UL) of 2,000 µg/day and should be safe for older adults.

Phosphorus

At present, there is no evidence that phosphorus requirements of older adults differ from that of younger adults, and a varied diet should easily provide the RDA (700 mg/day) of phosphorus for those over 50 years of age.

Potassium

A diet rich in fruit and vegetables that supplies 2.6-3.7 g/day of potassium is appropriate for healthy older adults because such diets are associated with decreased risk of stroke, hypertension, osteoporosis, and kidney stones. This recommendation does not apply to individuals who have been advised to limit potassium consumption by a health care professional (see the section on Safety in the article on potassium).

Selenium

Aging has not been associated with significant changes in the requirement for selenium. The Linus Pauling Institute supports the recommendation of the Food and Nutrition Board, which is 55 µg/day of selenium for adults of all ages. Although the amount of selenium in multivitamin/mineral supplements varies considerably, multivitamin/mineral supplements rarely provide more than the Daily Value (DV) of 70 µg. The average American diet is estimated to provide about 100 µg/day of selenium (15, 16). Thus, eating a varied diet and taking a daily multivitamin/mineral supplement should provide sufficient selenium for most adults in the US.

Sodium

There is consistent evidence that diets relatively low in salt (5.8 grams/day or less) and high in potassium are associated with decreased risk of high blood pressure and hypertension, as well as the associated risks of cardiovascular and kidney diseases. Diets low in sodium and rich in potassium are likely to be of particular benefit for older individuals, who are at increased risk of high blood pressure. Moreover, the Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet emphasizing fruit, vegetables, whole grains, nuts, and low-fat dairy products substantially lowered blood pressure, an effect that was enhanced by reducing salt intake to 5.8 grams/day or less. For more information on the DASH diet, see the article on Sodium. The Linus Pauling Institute recommends a diet that is rich in fruit and vegetables (at least 5 servings/day) and limits processed foods that are high in salt. Sensitivity to the blood pressure-raising effects of salt increases with age; therefore, consuming diets that are low in salt and high in potassium may especially benefit older adults.

Diets rich in potassium (≥2.6 g/day of potassium) and low in salt (5.8 grams/day or less) are likely to be of particular benefit for older adults, who are at increased risk of high blood pressure along with its associated risks of cardiovascular and kidney diseases. Since sensitivity to the blood pressure-raising effects of salt increases with age, consuming diets that are low in salt and high in potassium may especially benefit older adults.

Zinc

Although the requirement for zinc is not known to be higher for older adults, their average zinc intake tends to be considerably less than the RDA. A reduced capacity to absorb zinc, increased likelihood of disease states that alter zinc utilization, and increased use of drugs that increase zinc excretion may contribute to an increased risk of mild zinc deficiency in older adults. Because the consequences of mild zinc deficiency, such as impaired immune system function, are particularly relevant to the health of older adults, they should pay particular attention to maintaining adequate zinc intake.

Other nutrients

Choline

Little is known regarding the amount of dietary choline most likely to promote optimum health or prevent chronic disease in older adults. At present, there is no evidence to support a different intake of choline from that of younger adults (550 mg/day for men and 425 mg/day for women).

Essential fatty acids

α-Linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid, are considered essential fatty acids because they cannot be synthesized by humans. In 2002, the Food and Nutrition Board of the US Institute of Medicine established adequate intake (AI) levels for omega-6 and omega-3 fatty acids. Essential fatty acid recommendations for adults over the age of 50 are listed in **Table 2**. For more information on ALA and LA, see the article on Essential Fatty Acids.

Table 2. Adequate Intake (AI) for Essential Fatty Acids (17)

Essential Fatty Acid	Men	Women
ALA (>50 years)	1.6 g/day	1.1 g/day
LA (>50 years)	14 g/day	11 g/day

Abbreviations: ALA=α-linolenic acid; LA=linoleic acid; g=grams

International recommendations

Upon request of the European Commission, the European Food Safety Authority (EFSA) proposed adequate intakes (AI) for the essential fatty acids LA and ALA, as well as the long-chain omega-3 fatty acids EPA and DHA (18). EFSA recommends an LA intake of 4% of total energy and an ALA intake of 0.5% of total energy; an AI of 250 mg/day is recommended for EPA plus DHA.

The World Health Organization recommends an acceptable macronutrient distribution range (AMDR) for omega-6 fatty acid intake of 6-11% of energy and for omega-3 fatty acid intake of 0.5-2% of energy (19). Their AMDR for EPA plus DHA is 0.250-2 g/day (the upper limit applying to the secondary prevention of coronary heart disease).

The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommends for healthy adults an LA intake of 2% energy, ALA intake of 0.7% energy, and a minimum of 500 mg/day of EPA plus DHA for cardiovascular health (20).

American Heart Association recommendation

The American Heart Association recommends that people without documented coronary heart disease (CHD) eat a variety of fish (preferably oily) at least twice weekly (21). Two servings of oily fish provide approximately 500 mg of EPA plus DHA. People with documented CHD are advised to consume approximately 1 g/day of EPA + DHA preferably from oily fish, or to consider EPA + DHA supplements in consultation with a physician. Patients who need to lower serum triglycerides may take 2-4 g/day of EPA + DHA supplements under a physician's care.

Linus Pauling Institute recommendation

The Linus Pauling Institute recommends that generally healthy adults increase their intake of omega-3 fats by eating fish twice weekly and consuming foods rich in α-linolenic acid, such as walnuts, flaxseeds, and flaxseed or canola oil. If you don't regularly consume fish, consider taking a two-gram fish oil supplement several times a week. If you are prone to bleeding or take anticoagulant drugs, consult your physician.

Dietary factors

L-carnitine

Age-related declines in mitochondrial function and increases in mitochondrial oxidant production are thought to be important contributors to the adverse effects of aging. Tissue L-carnitine levels have been found to decline with age in humans and animals (22). One study found that feeding aged rats acetyl-L-carnitine (ALCAR) reversed the age-related declines in tissue L-carnitine levels and also reversed a number of age-related changes in liver mitochondrial function; however, high doses of ALCAR increased liver mitochondrial oxidant production (23). More recently, two studies found that supplementing aged rats with either ALCAR or lipoic acid, a mitochondrial cofactor and antioxidant, improved mitochondrial energy metabolism, decreased oxidative stress, and improved memory (24, 25). Interestingly, co-supplementation of ALCAR and lipoic acid resulted in even greater improvements than either compound administered alone. Likewise, several studies have reported that supplementing rats with both L-carnitine and lipoic acid blunts the age-related increases in reactive oxygen species (ROS), lipid peroxidation, protein carbonylation, and DNA strand breaks in a variety of tissues (heart, skeletal muscle, brain). Improvements in mitochondrial enzyme and respiratory chain activities were also observed (26-33). While these findings are very exciting, it is important to realize that these studies used relatively high doses (100 to 300 mg/kg body weight/day) of the compounds and only for a short time (one month). It is not yet known whether taking relatively high doses of these two naturally occurring substances will benefit rats in the long-term or will have similar effects in humans. Clinical trials in humans are planned, but it will be several years before the results are available. If you choose to take carnitine supplements, the Linus Pauling Institute recommends acetyl-L-carnitine at a daily dose of 500 to 1,000 mg.

Coenzyme Q_{10}

According to the free radical and mitochondrial theories of aging, oxidative damage of cell structures by reactive oxygen species (ROS) plays an important role in the functional declines that accompany aging (34). ROS are generated by mitochondria as a byproduct of ATP production. If not neutralized by antioxidants, ROS may damage mitochondria over time, causing them to function less efficiently and to generate more damaging ROS in a self-perpetuating cycle. Coenzyme Q_{10} plays an important role in mitochondrial ATP synthesis and functions as an antioxidant in mitochondrial membranes. Moreover, tissue levels of coenzyme Q_{10} have been reported to decline with age (35). One of the hallmarks of aging is a decline in energy metabolism in many tissues, especially liver, heart, and skeletal muscle. It has been proposed that age-associated declines in tissue coenzyme Q_{10} levels may play a role in this decline (36). In recent studies, lifelong dietary supplementation with coenzyme Q_{10} did not increase the life spans of rats or mice (37, 38); however, one study showed that coenzyme Q_{10} supplementation attenuates the age-related increase in DNA damage (39). Presently, there is no scientific evidence that coenzyme Q_{10} supplementation prolongs life or prevents age-related functional declines in humans.

Lipoic acid

Lipoic acid alone or in combination with other antioxidants or L-carnitine has been found to improve measures of memory in animal models of age-associated cognitive decline, including rats (24, 25), mice (40), and dogs (41). However, it is not clear whether oral lipoic acid supplementation can slow cognitive decline related to aging or other pathology in humans. An uncontrolled, open-label trial in nine patients with Alzheimer's disease and related dementias, who were also taking acetylcholinesterase inhibitors, reported that oral supplementation with 600 mg/day of racemic lipoic acid appeared to stabilize cognitive function over a one-year period (42). However, the significance of these findings is difficult to assess without a control group for comparison. A randomized controlled trial found that oral supplementation with 1,200 mg/day of racemic lipoic acid for 10 weeks was of no benefit in treating HIV-associated cognitive impairment (43). Although studies in animals suggest that lipoic acid may be helpful in slowing age-related cognitive decline, randomized controlled trials are needed to determine whether lipoic acid supplementation is effective in preventing or slowing cognitive decline associated with age or neurodegenerative disease. If you choose to take lipoic acid supplements, the Linus Pauling Institute recommends a daily dose of 200-400 mg/day of racemic lipoic acid for generally healthy people.

Flavonoids

The prevalence of several neurodegenerative diseases increases with advanced age. Inflammation, oxidative stress, and transition metal accumulation appear to play a role in the pathology of several neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. Because flavonoids have anti-inflammatory, antioxidant and metal-chelating properties, scientists are interested in the neuroprotective potential of flavonoid-rich diets or individual flavonoids. At present, the extent to which various dietary flavonoids and flavonoid metabolites cross the blood-brain barrier in humans is not known (44). Although flavonoid-rich diets and flavonoid administration have been found to prevent cognitive impairment associated with aging and inflammation in some animal studies (45-48), prospective cohort studies have not found consistent inverse associations between flavonoid intake and the risk of dementia or neurodegenerative disease in humans (49-53).

In a cohort of Japanese-American men followed for 25-30 years, flavonoid intake from tea during midlife was not associated with the risk of Alzheimer's or other types of dementia in late life (49). Surprisingly, higher intakes of isoflavone-rich tofu during midlife were associated with cognitive impairment and brain atrophy in late life (see the article on Soy Isoflavones) (50). A prospective study of Dutch adults found that total dietary flavonoid intake was not associated with the risk of developing Parkinson's disease (51) or Alzheimer's disease (52), except in current smokers whose risk of Alzheimer's disease decreased by 50% for every 12 mg increase in daily flavonoid intake. In contrast, a study of elderly French men and women found that those with the lowest flavonoid intakes had a risk of developing dementia over the next five years that was 50% higher than those with the highest intakes (53). More recently, a study in 1,640 elderly men and women found that those with higher dietary flavonoid intake (>13.6 mg/day) had better cognitive performance at baseline and experienced significantly less age-related cognitive decline over a 10-year period than those with a lower flavonoid intake (0-10.4 mg/day) (54). Additionally, a randomized, double-blind, placebo-controlled clinical trial in 202 postmenopausal women reported that daily supplementation with 25.6 g of soy protein (containing 99 mg of isoflavones) for one year did not improve cognitive function (55). However, a randomized, double-blind, placebo-controlled, cross-over trial in 77 postmenopausal women found that six-month supplementation with 60 mg/day of isoflavones improved some measures of cognitive performance (56). Although scientists are interested in the potential of flavonoids to protect the aging brain, it is not yet clear how flavonoid consumption affects neurodegenerative disease risk in humans.

Resveratrol

Caloric restriction is known to extend the lifespan of a number of species, including yeast, worms, flies, fish, rats, and mice (57). In yeast (Saccharomyces cerevisiae), caloric restriction stimulates the activity of an enzyme known as Silent information regulator 2 protein (Sir2) or sirtuin (58). Yeast Sir2 is a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase enzyme that removes the acetyl group from acetylated lysine residues in target proteins.

Providing resveratrol to yeast increased Sir2 activity in the absence of caloric restriction and extended the replicative (but not the chronological) lifespan of yeast by 70% (59). Resveratrol feeding also extended the lifespan of worms (*Caenorhabditis elegans*) and fruit flies (*Drosophila melanogaster*) by a similar mechanism (60). Additionally, resveratrol dose-dependently increased the lifespan of a vertebrate fish (*Nothobranchius furzeri*) (61). Resveratrol was also found to extend the lifespan of mice on a high-calorie diet such that their lifespan was similar to that of mice fed a standard diet 62. Although resveratrol increased the activity of the Sir2 homologous human sirtuin 1 (SIRT1) in the test tube (59), there are no epidemiological data to link resveratrol, SIRT1 activation, and extended human lifespan. Moreover, the supraphysiological concentrations of resveratrol required to increase human SIRT1 activity were considerably higher than concentrations that have been measured in human plasma after oral consumption.

The Linus Pauling Institute provides dietary and lifestyle recommendations for generally healthy individuals interested in optimum health and prevention of chronic diseases such as cardiovascular disease (heart disease and stroke), diabetes, cancer, and osteoporosis. These recommendations are contained in the Linus Pauling Institute's Rx for Health.

Disease Index

Click on a topic below for a list of related articles. Also see the Health & Disease section for content on cardiovascular disease, Alzheimer's disease, and osteoporosis.

- Micronutrients and Phytochemicals Related to Cognitive Decline
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- Micronutrients and Phytochemicals Related to Cardiovascular Disease
- Micronutrients and Phytochemicals Related to Cancer
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Glossary

Español

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Glossary: A

Acetylation
the addition of an acetyl group (-$COCH_3$) group to a molecule.

Achlorhydria
the absence of hydrochloric acid in gastric juice.

Acidic
having a pH of less than 7.

Acne vulgaris
a condition of the skin characterized by the presence of comedones.

Acrodermatitis enteropathica
a rare, inherited disorder of impaired zinc absorption.

Actinic lentigines
hyperpigmented patches that occur in sun-exposed skin; also known as liver spots or age spots.

Acute
having a short and relatively severe course.

Acute-phase reactant protein
also called acute-phase protein; plasma protein that is synthesized by the liver during acute inflammation. Examples include C-reactive protein (CRP), fibrinogen, serum amyloid A protein, and von Willebrand factor.

Action potential
the electrochemical signal transmitted in the cell membrane of a neuron or muscle cell. Also called nerve impulse.

Adipose tissue
specialized connective tissue that functions to store body fat as triglycerides.

Adjunct therapy
a treatment or therapy used in addition to another, not alone.

Adrenal glands
a pair of small glands, located above the kidneys, consisting of an outer cortex and inner medulla. The adrenal cortex secretes cortisone-related hormones and the adrenal medulla secretes epinephrine (adrenaline) and norepinephrine (noradrenaline).

Aglycone
the nonsugar component of a glycoside. Cleavage of the glycosidic bond of a glycoside results in the formation of a sugar and an aglycone.

AI
adequate intake. Established by the Food and Nutrition Board of the US Institute of Medicine, the AI is a recommended intake value based on observed or experimentally determined estimates of nutrient intake by a group of healthy people that are assumed to be adequate. An AI is established when an RDA cannot be determined.

AIDS
acquired immune deficiency syndrome. AIDS is caused by the HIV (Human Immunodeficiency Virus) virus, which attacks the immune system, leaving the infected individual vulnerable to opportunistic infections.

Alkaline
basic; having a pH of more than 7.

Alkaloid
a plant-derived compound that is biologically active, contains a nitrogen in a heterocyclic ring, is alkaline, has a complex structure, and is of limited distribution in the plant kingdom.

Allele
one of a set of alternative forms of a gene. Diploid cells possess two homologous chromosomes (one derived from each parent) and therefore two copies of each gene. In a diploid cell, a gene will have two alleles, each occupying the same position on homologous chromosomes.

Alopecia
loss of hair.

Alzheimer's disease
the most common cause of dementia in older adults. Alzheimer's disease is characterized by the formation of amyloid plaque in the brain and nerve cell degeneration. Symptoms include memory loss and confusion, which worsen over time.

Amino acid
an organic molecule that contains an amino group (-NH_2) and a carboxyl group (-COOH); amino acids are as the building blocks of proteins.

AMP
adenosine monophosphate. A important compound in energy metabolism. Addition of two phosphates to AMP forms ATP.

Amphipathic
a chemical compound having both hydrophilic (water-loving, polar) and lipophilic (fat-loving, nonpolar) properties.

Amyloid plaque
aggregates of a peptide called amyloid-β, which accumulate and form deposits in the brain in Alzheimer's disease.

Amyotrophic lateral sclerosis (ALS)
a rapidly progressive and fatal neurological disease caused by degeneration of motor neurons that control voluntary muscle movement. Also known as Lou Gehrig's disease.

Anabolism
the synthesis of large complex molecules from simple molecules.

Anaerobic
refers to the absence of oxygen or the absence of a need for oxygen.

Analog
a chemical compound that is structurally similar to another but differs slightly in composition (e.g., the replacement of one functional group by another).

Anaphylaxis
a rapidly developing and severe systemic allergic reaction. Symptoms may include swelling of the tongue, throat, and trachea, which can result in difficulty breathing, shock and loss of consciousness. If not treated rapidly, anaphylaxis can be fatal.

Anemia
the condition of having less than the normal number of red blood cells or hemoglobin in the blood, resulting in diminished oxygen transport. Anemia has many cause, including iron, vitamin B_{12}, or folate deficiency; bleeding; abnormal hemoglobin formation (e.g., sickle cell anemia); rupture of red blood cells (hemolytic anemia); and bone marrow diseases.

Anencephaly
a birth defect, known as a neural tube defect, resulting from failure of the upper end of the neural tube to close during embryonic development. Anencephaly is a devastating and sometimes fatal birth defect resulting in the absence of most or all of the cerebral hemispheres.

Angina pectoris
pain generally experienced in the chest, but sometimes radiating to the arms or jaw, due to a lack of oxygen supply to the heart muscle.

Angiogenesis
the development of new blood vessels.

Angiography (coronary)
imaging of the coronary arteries used to identify the location and severity of any obstructions. Coronary angiography typically involves the administration of a contrast medium and imaging of the coronary arteries using an X-ray based technique.

Anion
a negatively charged ion.

Anotia
the absence of the external ear.

Antagonist
a substance that counteracts or nullifies the biological effects of another, such as a compound that binds to a receptor but does not elicit a biological response.

Antenatal
before birth; also called prenatal.

Anthropometric
relating to the measurement of the human body.

Antibody
a specialized protein produced by white blood cells (lymphocytes) that recognizes and binds to foreign proteins or pathogens in order to neutralize them or mark them for destruction.

Anticoagulant
a class of compounds that inhibit blood clotting.

Anticonvulsant
a class of medication used to prevent seizures.

Antigen
a substance that is capable of eliciting an immune response.

Antihistamine
a chemical that blocks the effect of histamine in a susceptible tissues. Histamine is released by immune cells during an allergic reaction and also during infection with viruses that cause the common cold. The interaction of histamine with the mucus membranes of the eyes and nose results in "watery eyes" and the "runny nose" often accompanying allergies and colds. Antihistamines can help alleviate such symptoms.

Antimicrobial
capable of killing or inhibiting the growth of microorganisms, such as bacteria.

Antioxidant
any substance that prevents or reduces damage caused by reactive oxygen species (ROS) or reactive nitrogen species (RNS).

Antiresorptive agent
a medication or hormone that inhibits bone resorption.

Anxiolytic
an agent that decreases anxiety.

Apgar score
a scoring system used to assess the physical condition of a newborn immediately after birth. Criteria evaluated include respiratory effort, heart rate, skin coloration, muscle tone, and response to stimulation.

Apoptosis
gene-directed cell death or programmed cell death that occurs when age, condition, or state of cell health dictates. Cells that die by apoptosis do not usually elicit the inflammatory responses that are associated with necrosis. Cancer cells are resistant to apoptosis.

Aqueous
referring to water or a solution containing water.

Arrhythmia
an abnormal heart rhythm. The heart rhythm may be too fast (tachycardia), too slow (bradycardia) or irregular. Some arrhythmias, such as ventricular fibrillation, may lead to cardiac arrest if not treated promptly.

Asphyxia
a lack of oxygen or excess carbon dioxide in the body that causes unconsciousness.

Asthma
a chronic inflammatory disease of the airways, characterized by recurrent episodes of reversible airflow obstruction.

Astrocyte
a type of glial cell in the central nervous system.

Ataxia
a lack of coordination or unsteadiness usually related to a disturbance in the cerebellum, a part of the brain that regulates coordination and equilibrium.

Atherogenic
capable of producing atherosclerosis.

Atherosclerosis
an inflammatory disease resulting in the accumulation of cholesterol-laden plaque in artery walls. Rupture of atherosclerotic plaque results in clot formation, which may result in myocardial infarction or ischemic stroke.

ATP
adenosine triphosphate. An important compound for the storage of energy in cells, as well as the synthesis of nucleic acids.

Atria
(singular: atrium) two upper chambers of the heart that receive blood from the veins and contract to force that blood into the ventricles.

Atrial fibrillation
a cardiac arrhythmia, characterized by rapid, uncoordinated beating of the atria, which results in ineffective atrial contractions. Atrial fibrillation is known as a supraventricular arrhythmia because it originates above the ventricles.

Atrophic gastritis
a chronic inflammation of the lining of the stomach, which ultimately results in the loss of glands in the stomach (atrophy) and decreased stomach acid production.

Atrophy
a decrease in size or wasting away of a body part or tissue.

Attrition
a reduction in number.

Autoimmune disease
a condition in which the body's immune system reacts against its own tissues.

Autophosphorylation
the phosphorylation by a protein of one or more of its own amino acid residues. Autophosphorylation does not necessarily occur on the same polypeptide chain as the catalytic site. In a dimer, one subunit may phosphorylate the other.

Autosomal

refers to a trait or gene that is not located on the X or Y chromosome (not sex-linked).

Axon
long extension of a neuron that transmits nerve impulses away from the cell body toward other neurons or muscle cells.

Glossary B:

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Bacteria
single-celled organisms that can exist independently, symbiotically (in cooperation with another organism) or parasitically (dependent upon another organism, sometimes to the detriment of the other organism). Examples of bacteria include acidophilus (found in yogurt); streptococcus the cause of strep throat; and E. coli (a normal intestinal bacteria, as well as a disease-causing agent).

Balance study
a nutritional balance study involves the measurement of the intake of a specific nutrient as well as the elimination of that nutrient in urine, feces, sweat, etc. If intake is greater than loss of a particular nutrient the individual is said to be in "positive balance." If intake is less than loss, an individual is said to be in "negative balance" for the nutrient of interest.

Bariatrics
the branch of medicine that relates to the treatment of obesity.

Benign
not malignant.

Benign prostatic hyperplasia
the term used to describe a noncancerous enlargement of the prostate.

Bias
any systematic error in an epidemiological study that results in an incorrect estimate of the association between an exposure and disease risk.

Bile
a yellow, green fluid made in the liver and stored in the gallbladder. Bile may then pass through the common bile duct into the small intestine where some of its components aid in the digestion of fat.

Bile acids
components of bile, which are formed by the metabolism of cholesterol, and aid in the digestion of fats.

Bioavailability
the fraction of an administered compound that reaches the systemic circulation and is transported to site of action (target tissue).

Biomarker
a physical, functional, or biochemical indicator of a physiological or disease process.

Biotransformation enzymes (phase I and phase II)
enzymes involved in the metabolism and elimination of a variety of exogenous (drugs, toxins and carcinogens) and endogenous compounds (steroid hormones). In general, phase I biotransformation enzymes, including those of the cytochrome P450 family, catalyze reactions that increase the reactivity of fat-soluble compounds and prepare them for reactions catalyzed by phase II biotransformation enzymes. Reactions catalyzed by phase II enzymes generally increase water solubility and promote the elimination of these compounds.

Bipolar disorder
a mood disorder previously called “manic-depressive illness.” Bipolar disorder is characterized by severe alterations in mood. During “manic” episodes, a person may experience extreme elevation in energy level and mood (euphoria) or extreme agitation and irritability. Episodes of depressed mood are also common in bipolar disorder.

Body mass index (BMI)
body weight in kilograms divided by height in meters squared. In adults, BMI is a measure of body fat: underweight, <18.5; normal weight, 18.5-24.9; overweight, 25-29.9; obese, ≥30. Calculate your BMI.

Bone mineral density (BMD)
the amount of mineral in a given area of bone. BMD is positively associated with bone strength and resistance to fracture, and measurements of BMD are used to diagnose osteoporosis.

Bone remodeling
the continuous turnover process of bone that includes bone resorption and bone formation. An imbalance in the regulation of the two contrasting events of bone remodeling (bone resorption and bone formation) increases the fragility of bone and may lead to osteoporosis.

Borborygmus
a rumbling sound caused by gas movement in the intestines; sometimes called "stomach rumble."

Branched-chain amino acids
the essential amino acids: leucine, isoleucine, and valine.

Bronchitis, chronic
long-standing inflammation of the airways, characterized by excess production of sputum, leading to a chronic cough and obstruction of air flow. Cigarette smoking is the most common cause of chronic bronchitis.

Buffer
a chemical used to maintain the pH of a system by absorbing hydrogen ions (which would make it more acidic) or absorbing hydroxyl ions (which would make it more alkaline).

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C-reactive protein (CRP)
a protein that is produced in the liver in response to inflammation. CRP is a biomarker of inflammation that is strongly associated with the risk of cardiovascular events, such as myocardial infarction and stroke.

Calcification
the process of deposition of calcium salts. In the formation of bone this is a normal condition. In other organs, this could be an abnormal condition; for example, calcification of the aortic valve causes narrowing of the passage (aortic stenosis).

Cancer
refers to abnormal cells, which have a tendency to grow uncontrollably and metastasize or spread to other areas of the body. Cancer can involve any tissue of the body and can have different forms in one tissue. Cancer is a group of more than 100 different diseases.

Carbohydrate
considered a macronutrient because carbohydrates provide a significant source of calories (energy) in the diet. Chemically, carbohydrates are neutral compounds composed of carbon, hydrogen and oxygen. Carbohydrates come in simple forms known as sugars and complex forms, such as starches and fiber.

Carboxylase
an enzyme that catalyzes carboxylation reactions.

Carboxylation
the introduction of a carboxyl group (-COOH) or carbon dioxide into a compound.

Carcinogen
a cancer-causing agent; adjective: carcinogenic.

Carcinogenesis
the formation of cancer cells from normal cells.

Carcinoid syndrome
the pattern of symptoms exhibited by individuals with carcinoid tumors. Carcinoid tumors secrete excessive amounts of the neurotransmitter, serotonin. Symptoms may include flushing, diarrhea, and sometimes wheezing.

Cardiac output
volume of blood pumped by the heart in a specified time period.

Cardiomyopathy
literally, disease of the heart muscle that often leads to abnormal function.

Cardiovascular
referring to the heart and blood vessels.

Cardiovascular disease
literally, diseases affecting the heart and blood vessels. The term has come to encompass a number of conditions that result from atherosclerosis, including myocardial infarction (heart attack), congestive heart failure, and stroke.

Carnitine
a compound that is required to transport long-chain fatty acids across the inner membrane of the mitochondria, in the form of acyl-carnitine, where they can be metabolized for energy.

Carotid arteries
the left and right common carotid arteries are the principal blood vessels that supply oxygenated blood to the head and neck. Each has two main branches, the external and internal carotid artery.

Cartilage
a soft, elastic tissue that composes most of the skeleton of vertebrate embryos and except for a small number of structures is replaced by bone during ossification in the higher vertebrates. Cartilage cushions joints, connects muscles with bones, and makes up other parts of the body, such as the larynx (voice box) and the outside portion of the ears.

Case-control study
a study in which exposures of people who have been diagnosed with a disease (cases) are compared to those of people without the disease (controls). The results of case-control studies are more likely to be distorted by bias in the selection of cases and controls (selection bias) and dietary recall (recall bias) than prospective cohort studies.

Case report
a report that decribes an individual case of a disease or medical condition. This type of research cannot indicate causality but may indicate areas for further research.

Catabolism
the breakdown of complex molecules into smaller ones, accompanied by the release of energy.

Catalyze
to increase the speed of a chemical reaction without being changed in the overall reaction process. See enzyme.

Cataract
clouding of the lens of the eye. As cataracts progress, they can impair vision.

Catecholamine
a substance with a specific chemical structure (a benzene ring with two adjacent hydroxyl groups and a side chain of ethylamine) that functions as a hormone or neurotransmitter. Examples include epinephrine, norepinephrine, and dopamine.

Cation
a positively charged ion.

Celiac disease
also known as celiac sprue, celiac disease is an inherited disease in which the intestinal lining is inflamed in response to the ingestion of a protein known as gluten. Treatment of celiac disease involves the avoidance of gluten, which is present in many grains, including wheat, rye, oats, and barley. Inflammation and atrophy of the lining of the small intestine leads to impaired nutrient absorption.

Cell adhesion molecule
a molecule on the outside surface of cells that binds to other cells or to the extracellular matrix (material surrounding cells). Cell adhesion molecules influence many important functions, including the entry of immune cells into the arterial wall.

Cell cycle
the orderly sequence of stages that a cell passes through between one cell division (mitosis) and the next. The cell cycle can be divided into four stages: the M (mitosis) phase, in which nuclear and cytoplasmic division occurs; the G1 phase or interphase; the S (synthesis) phase, in which DNA replication occurs; and the G2 phase, a quiescent period prior to the next M phase.

Cell membrane
also called a plasma membrane; the barrier that separates the contents of a cell from its outside environment and controls what moves in and out of the cell. A mammalian cell membrane consists of a phospholipid bilayer with embedded proteins and cholesterol.

Cell signaling
communication among individual cells so as to coordinate their behavior to benefit the organism as a whole. Cell-signaling systems elucidated in animal cells include cell-surface and intracellular receptor proteins, GTP-binding proteins, as well as protein kinases and protein phosphatases (enzymes that phosphorylate and dephosphorylate proteins).

Central nervous system (CNS)
the brain, spinal cord, and spinal nerves.

Ceramide
a specialized type of lipid comprised of a sphingosine backbone with fatty acid side chains. Ceramides function as signaling molecules and are critical structural components in cell membranes.

Cerebral
relating to the brain.

Cerebrospinal fluid
the fluid that bathes the brain and spinal cord.

Cerebrovascular disease
disease involving the blood vessels supplying the brain, including cerebrovascular accident (CVA), also known as a stroke.

Cerebrum
the upper part of the brain that is involved in conscious mental functions.

Ceruloplasmin
a ferroxidase enzyme that has the capacity to oxidize ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), which can be loaded onto the iron-transport protein, transferrin.

Cervical intraepithelial neoplasia (CIN)
a term used to describe abnormal growth of cells on the surface of the uterine cervix. CIN1 is also known as low-grade squamous intraepithelial lesion (LSIL). CIN2 and CIN3 are also known as high-grade squamous intraepithelial lesions (HSIL). Although these abnormal cells are not cancerous, they may progress to cervical cancer.

Chelate
the combination of a metal with an organic molecule to form a ring-like structure known as a chelate. Chelation of a metal may inhibit or enhance its bioavailability.

Chemotaxis
movement of a cell or organism toward or away from a chemical stimulus.

Chemotherapy
literally, treatment with drugs. Commonly used to describe the systemic use of drugs to kill cancer cells, as a form of cancer treatment.

Cholecystectomy
removal of the gallbladder.

Cholestatic liver disease
liver disease resulting in the cessation of bile excretion. Cholestasis may occur in the liver, gallbladder, or bile duct (duct connecting the gall bladder to the small intestine).

Cholesterol
a compound that is an integral structural component of cell membranes and a precursor in the synthesis of steroid hormones. Dietary cholesterol is obtained from animal sources, but cholesterol is also synthesized by the liver. Cholesterol is carried in the blood by lipoproteins. In atherosclerosis, cholesterol accumulates in plaques on the walls of some arteries.

Cholinergic
resembling acetylcholine in action, a cholinergic drug for example. Cholinergic nerve fibers liberate or are activated by the neurotransmitter, acetylcholine.

Chorionic villus sampling (CVS)
a procedure for obtaining a small sample of tissue from the placenta (chorionic villi) for the purpose of prenatal diagnosis of genetic disorders. CVS can be performed between 9 to 12 weeks of pregnancy.

Chromatin
complex of DNA, RNA, and proteins that comprise chromosomes.

Chromosome
a structure in the nucleus of a cell that contains genes. Chromosomes are composed of DNA and associated proteins. Normal human cells contain 46 chromosomes (22 pairs of autosomes and 2 sex chromosomes).

Chronic disease
an illness lasting a long time. By definition of the US Center for Health Statistics, a chronic disease is a disease lasting three months or more.

Chronic obstructive pulmonary disease (COPD)
a term that includes emphysema and chronic bronchitis, two chronic lung diseases that are characterized by airway obstruction.

Chylomicrons
triglyceride-rich lipoproteins that deliver dietary triglycerides from the intestine to the tissues immediately after a meal. Chylomicrons release their triglycerides to tissue through the activity of lipoprotein lipase enzymes in tissue capillary beds. When they are depleted of most of their triglycerides, chylomicron remnants are taken up by the liver, where the lipids and cholesterol that remain are excreted in bile or incorporated into other lipoproteins.

Chyme
the mass of partially digested food that exits the stomach and enters the duodenum of the small intestine.

Cirrhosis
a condition characterized by irreversible scarring of the liver, leading to abnormal liver function. Cirrhosis has a number of different causes, including chronic alcohol use and viral hepatitis B and C.

Citric acid cycle
the metabolic pathway in the mitochondria that oxidizes acetyl compounds form food to carbon dioxide and water. Also referred to as the Krebs cycle and the tricarboxylic acid (TCA) cycle.

Clinical trial
an intervention trial generally used to evaluate the efficacy and/or safety of a treatment or intervention in human participants.

Clone
an exact copy of a DNA segment; produced by recombinant DNA technology.

Coagulation
the process involved in blood clot formation.

Coenzyme
a molecule that binds to an enzyme and is essential for its activity but is not permanently altered by the reaction. Many coenzymes are derived from vitamins.

Cofactor
a compound that is essential for the activity of an enzyme.

Cognition
mental process of thought; includes brain functions like attention, memory, planning, developing strategies, and problem solving.

Cognitive
referring to the processes of cognition.

Cohort
a group of people who are followed over time as part of an epidemiological study.

Cohort study
a study that follows a large group of people over a long period of time, often 10 years or more. In cohort studies, dietary information is gathered before disease occurs, rather than relying on recall after disease develops.

Collagen
a fibrous protein that is the basis for the structure of skin, tendon, bone, cartilage and all other connective tissue.

Collagenous matrix (of bone)
the organic (nonmineral) structural element of bone. Collagen is a fibrous protein that provides the organic matrix upon which bone mineralize crystallizes.

Colon
the portion of the large intestine that extends from the end of the small intestine to the rectum. The colon removes water from digested food after it has passed through the small intestine and stores the remaining stool until it can be evacuated.

Colorectal adenoma
a polyp or growth in the lining of the colon or rectum. Although they are not cancerous, colorectal adenomas may develop into colorectal cancer over time.

Colorectal cancer
cancer of the colon (large intestine) or rectum.

Colostomy
the surgical construction of an artificial anus by connecting the colon to an opening in the abdominal wall.

Comedone
a pilosebaceous unit blocked with sebum and inflammatory cells.

Complement
system of serum proteins that function to help destroy invading microorganisms.

Concomitant
accompanying. "Concomitant intake" refers to the intake of two compounds at the same time.

Conditionally essential nutrient
although not strictly considered a nutrient due to endogenous synthesis, certain conditions (e.g., stress, aging) may result in the demand exceeding the body's capacity for synthesis, rendering a conditionally essential nutrient.

Confidence interval (CI)
a statistical measure of certainty. A CI defines the range within which we can be certain that a result is not due to chance alone.

Confounder
an extraneous factor in an observational study that distorts or biases an association between an exposure and the measured outcome. Confounders are associated with the exposure and outcome of interest, but they are not in the causal pathway.

Congenital anomaly
a birth defect, a condition present at birth.

Congenital hypothyroidism
deficiency of thyroid gland activity in newborn infants.

Congenital malformation
birth defects.

Congestive heart failure (CHF)
a condition, in which the heart loses the ability to pump blood efficiently enough to meet the demands of the body. Symptoms may include edema (swelling), shortness of breath, weakness and exercise intolerance.

Conjugate
a compound formed through joining (conjugation) of at least two chemical compounds.

Conjugation
the formation of a water-soluble derivative of a chemical by its combination with another compound, such as glutathione, glucuronate, or sulfate.

Cornea
the transparent covering of the front of the eye that transmits and focuses light into the eye.

Corneocyte
a metabolically inactive, flattened cell of the stratum corneum. Corneocytes are formed from keratinocytes in a process termed cornification. Corneocytes are metabolically inactive and will eventually be cast off from the body when new corneocytes are generated underneath them.

Cornification
the process by which a keratinocyte becomes a corneocyte in the outer, visible layer of the epidermis. This is marked by a loss of intracellular organelles, the production of specialized proteins and lipids, and the generation of a thick protein envelope just inside the cell membrane. Corneocytes are metabolically inactive and will eventually be cast off from the body when new corneocytes are generated underneath them.

Coronary angioplasty
a procedure used to open an occluded coronary artery. A flexible hollow catheter is inserted into a large blood vessel in the groin and advanced to the heart. At the site of the occlusion, the balloon tip of the catheter is inflated and the occluded coronary artery is dilated. Coronary angioplasty is also known as percutaneous transluminal coronary angioplasty or PTCA.

Coronary artery
one of the vessels that supply oxygenated blood to the heart muscle itself. They are called coronary arteries because they encircle the heart in the form of a crown.

Coronary artery bypass graft (CABG)
a surgical procedure used to create new routes around obstructions in coronary arteries and restore adequate blood flow to the heart muscle.

Coronary heart disease (CHD)
sometimes called coronary artery disease or coronary disease, coronary heart disease is the result of atherosclerosis of the coronary arteries. Atherosclerosis may result in narrowing or blockage of the coronary arteries and is the underlying cause of myocardial infarction (heart attack).

Cortical bone
also known as compact bone, the type of bone that forms the outer surface of all bones. The small bones of the wrists, hands, and feet are entirely cortical bone.

Corticosteroid
any of the steroid hormones made by the cortex (outer layer) of the adrenal gland. Cortisol is a corticosteroid. A number of medications are analogs of natural corticosteroid hormones.

Covalent bond
a chemical bond in which electrons are shared between atoms.

Craniosynostosis
abnormal skull shape due to the fibrous sutures of the skull having turned into bone prematurely.

Creatine phosphate
a high-energy compound found in muscle cells, which is used to convert ADP into ATP by donating phosphate molecules to the ADP. ATP is the molecule that is converted into ADP with a release of energy that the body then uses.

Cretinism
a condition that can result from a severe form of congenital hypothyroidism. Cretinism occurs in two forms, although there is considerable overlap. The neurologic form is characterized by mental and physical retardation and deafness. It is the result of maternal iodine deficiency that affects the fetus before its own thyroid is functional. The myxedematous or hypothyroid form is characterized by short stature and mental retardation. In addition to iodine deficiency, the hypothyroid form has been associated with selenium deficiency and the presence of goitrogens in the diet that interfere with thyroid hormone production.

Crohn's disease
an inflammatory bowel disease that usually affects the lower part of the small intestine or upper part of the colon but may affect any part of the gastrointestinal tract.

Cross-over trial
a clinical trial where at least two interventions or treatments are applied to the same individuals after an appropriate wash-out period. One of the treatments is often a placebo. In a randomized cross-over design, interventions are applied in a randomized order to ensure that the order of treatments did not contribute to the outcome.

Cross-sectional study
a study of a group of people at one point in time to determine whether an exposure is associated with the occurrence of a disease. Because the disease outcome and the exposure (e.g., nutrient intake) are measured at the same time, a cross-sectional study provides a “snapshot” view of their relationship. Cross-sectional studies cannot provide information about causality.

Cutaneous
related to or affecting the skin.

Cystic fibrosis (CF)
a hereditary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTCR) gene. Cystic fibrosis is characterized by the production of abnormal secretions, leading to the accumulation of mucus in the lungs, pancreas, and intestine. This build-up of mucus causes difficulty breathing and recurrent lung infections, as well as problems with nutrient absorption due to problems in the pancreas and intestines.

Cytochrome P450
a family of phase I biotransformation enzymes that play an important role in the metabolism and elimination of drugs, toxins, carcinogens, and endogenous compounds, such as steroid hormones.

Cytokine
a protein made by cells that affects the behavior of other cells. Cytokines act on specific cytokine receptors in the cells they affect.

Cytoplasm
the contents of a cell, excluding the nucleus.

Cytosol
the water-soluble contents of a cell's cytoplasm, excluding the organelles.

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De novo synthesis
the formation of an essential molecule from simple precursor molecules.

Debridement
the removal of necrotic or infected tissue or foreign material from a wound.

Decarboxylation
a chemical reaction involving the removal of a carboxyl (-COOH) group from a compound.

Dementia
significant impairment of intellectual abilities, such as attention, orientation, memory, judgment or language. By definition, dementia is not due to major depression or psychosis. Alzheimer’s disease is the most common cause of dementia in older adults.

Dendrite
a branched extension of a neuron that receives signals from other neurons.

Dendritic cell
an immune cell that functions in antigen presentation and activation of T lymphocytes. Dendritic cells have a branched morphology that resembles dendrites of a neuron.

Dental caries
cavities or holes in the outer two layers of a tooth—the enamel and the dentin. Dental caries are caused by bacteria, which metabolize carbohydrates (sugars) to form organic acids that dissolve tooth enamel.

Depletion-repletion study
a nutritional study designed to determine the requirement for a specific nutrient. Generally, subjects are placed on a diet designed to deplete them of a specific nutrient over time. Once depletion is achieved, gradually increasing amounts of the nutrient under study are added to the diet until the individual shows evidence of sufficiency or repletion.

Dermatitis
inflammation of the skin. This term is often used to describe a skin rash.

Dermatoses
any skin disease, especially one not characterized by inflammation.

Dermis
the layers of skin below the epidermis that support the epidermis in both structure and function. Although the majority of cells in this layer are fibroblasts supported by a collagen network, blood vessels, immune cells, and adipose tissue are also found in the dermis.

DEXA or DXA
dual-energy X-ray absorptiometry. A precise instrument that uses the energy from very small doses of X-rays to determine bone mineral density (BMD) and to diagnose and follow the treatment of osteoporosis.

Diabetes mellitus
a chronic metabolic disease, characterized by abnormally high blood glucose (sugar) levels, resulting from the inability of the body to produce or respond to insulin. Type 1 diabetes mellitus, formerly known as insulin-dependent or juvenile-onset diabetes, is usually the result of autoimmune destruction of the insulin secreting β-cells of the pancreas. The most common form of diabetes is type 2 diabetes mellitus, formerly known as noninsulin-dependent or adult onset diabetes, which develops when the tissues of the body become less sensitive to insulin secreted by the pancreas.

Diabetic ketoacidosis
a potentially life-threatening condition characterized by ketosis (elevated levels of ketone bodies in the blood) and acidosis (increased acidity of the blood). Ketoacidosis occurs when diabetes is not adequately controlled.

Dialysis
a medical procedure to filter waste products from the blood. Dialysis is needed to perform the work of the kidneys if they can no longer function effectively. Two types of dialysis are hemodialysis and peritoneal dialysis.

Diastolic blood pressure
the lowest arterial blood pressure during the heart beat cycle, and the second number in a blood pressure reading (e.g., 120/80).

Differentiation
changes in a cell resulting in its specialization for specific functions, such as those of a nerve cell. In general, differentiation of cells leads to a decrease in proliferation.

Diffusion
a passive process, in which particles in solution move from a region of higher concentration to one of lower concentration.

Dimer
a complex of two molecules, usually proteins. Heterodimers are complexes of two different molecules, while homodimers are complexes of two of the same molecule.

Diuretic
an agent that increases the formation of urine by the kidneys, resulting in water loss from the individual using the diuretic.

Diverticulitis
inflammation or infection of diverticula in the colon (see diverticulosis), characterized by abdominal pain, fever, and constipation.

Diverticulosis
a condition characterized by the formation of small pouches (diverticula) in the colon. Although most people with diverticulosis experience no symptoms, about 15-20% may develop pain or inflammation, known as diverticulitis.

DNA
deoxyribonucleic acid; a double-stranded nucleic acid composed of many nucleotides. The nucleotides in DNA are each composed of a nitrogen-containing base (adenine, guanine, cytosine, or thymine), a five-carbon sugar (deoxyribose), and a phosphate group. The sequence of bases in DNA encodes the genetic information required to synthesize proteins.

DNA adduct
the complex formed when a chemical forms a covalent bond with DNA.

Dominant trait
a trait that is expressed when only one copy of the gene responsible for the trait is present.

Double-blind
refers to a study in which neither the investigators administering the treatment nor the participants know which participants are receiving the experimental treatment and which are receiving the placebo.

DRI
dietary reference intake. Refers to a set of at least four nutrient-based reference values (RDA, AI, UL, EAR), each with a specific use in defining recommended dietary intake levels for individual nutrients in the US. The DRIs are determined by expert panels appointed by the Food and Nutrition Board of the Institute of Medicine.

DV
daily value. Refers to the dietary reference values required as the basis for declaring nutrient content on all products regulated by the US Food and Drug Administration (FDA), including nutritional supplements. The DVs for vitamins and minerals reflect the National Academy of Sciences' 1968 RDAs, and do not reflect the most up-to-date Dietary Reference Intakes.

Dysbiosis
an imbalance of intestinal microbiota.

Dyskinesia
impaired control of voluntary movement. Dyskinesia is sometimes a side effect of long-term use of antipsychotic medications.

Dyslipidemia
a disorder of lipoprotein metabolism.

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EAR
estimated average requirement; a nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a particular life stage and gender group.

Echocardiography
a diagnostic test that uses ultrasound to make images of the heart. It can be used to assess the health of the valves and chambers of the heart, as well as to measure cardiac output.

Eclampsia
seizures in a woman caused by pregnancy-induced hypertension; a significant cause of maternal mortality.

Ecologic study
an epidemiological study that examines the relationships between exposures and disease rates in a series of populations (e.g., different countries). Ecologic studies often rely on published statistics, such as food disappearance data or disease-specific death rates.

Edema
swelling; accumulation of excessive fluid in subcutaneous tissues (beneath the skin).

Eicosanoid
a chemical messenger derived from a 20-carbon polyunsaturated fatty acid, such as arachidonic acid and eicosapentaenoic acid. Eicosanoids play critical roles in immune and inflammatory responses.

Elastin
a flexible structural protein similar to collagen; elastin is found in the dermal layer of skin and other parts of the body.

Electrocardiogram (ECG)
a recording of the electrical activity of the heart, used to diagnose cardiac arrhythmias, myocardial ischemia and myocardial infarction.

Electroencephalogram (EEG)
a recording of the electrical activity of the brain, used to diagnose neurological conditions like seizure disorders (epilepsy).

Electrolytes
ionized (dissociated into positive and negative ions) salts in the body fluids. Major electrolytes in the body include sodium, potassium, magnesium, calcium, chloride, bicarbonate, and phosphate.

Electron
a stable atomic particle with a negative charge.

Electron transport chain
a group of electron carriers in mitochondria that transport electrons to and from each other in a sequence, in order to generate ATP.

Element
one of the 103 chemical substances that cannot be divided into simpler substances by chemical means. For example, hydrogen, magnesium, lead, and uranium are all chemical elements. Trace elements are chemical elements that are required in very small (trace) amounts in the diet to maintain health. For example, copper, selenium, and iodine are considered trace elements.

Emphysema
a chronic obstructive pulmonary (lung) disease, characterized by damage to the small air sacs (alveoli) and difficulty breathing. Damage to the alveoli decreases their elasticity and results in hyperinflation of the lungs, which impairs gas exchange. Smoking is the most common cause of emphysema.

Enamel
the hard, white, outermost layer of a tooth.

Enantiomer
either of two optical isomers that are mirror images of each other.

Encephalopathy
a disease of the brain that alters brain function.

Endocrine system
the glands and parts of glands that secrete hormones that integrate and control the body's metabolic activity. Endocrine glands include the pituitary, thyroid, parathyroids, adrenals, pancreas, ovaries, and testes.

Endocytosis
A type of cellular uptake that involves invagination of the cell membrane at the site of ligand binding followed by internalization of the substance inside a membrane-bound vesicle.

Endogenous
arising from within the body. Endogenous synthesis refers to the synthesis of a compound by the body.

Endometrium
the inner lining of the uterus.

Endothelium-dependent vasodilation
arterial vasodilation resulting from the production of nitric oxide in the vascular endothelium.

Endotoxin
toxins released by certain bacteria.

Enrichment
the addition of nutrients to replace losses that may occur in food processing.

Enterocyte
a cell that lines the luminal (inner) surface of the intestine.

Enzyme
a biological catalyst; that is, a substance that increases the speed of a chemical reaction without being changed in the overall process. Enzymes are vitally important to the regulation of the chemistry of cells and organisms.

Epidemiological study
a study examining disease occurrence in a human population.

Epidermis
the outer layers of skin above the dermis. The epidermis consists of overlapping layers of keratinocytes in various stages of development, eventually forming the barrier that protects underlying cell layers from the environment.

Epididymis
a system of tubules emerging from the testes, which serves as a storage site for sperm during their maturation.

Epilepsy
also known as seizure disorder. Individuals with epilepsy experience seizures, which are the result of uncontrolled electrical activity in the brain. A seizure may cause a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms.

Epithelium
layer of cells that lines a body cavity or covers an external surface of the body.

Erythema
reddening of the skin; often used as an indice of inflammation caused by ultraviolet exposure.

Erythrocyte
red blood cell.

Erythroid
relating to erythrocytes.

Erythropoiesis
the production of red blood cells.

Erythropoietin
a hormone produced by specialized cells in the kidneys that stimulates the bone marrow to increase the production of red blood cells. Recombinant erythropoietin is used to treat anemia in patients with end stage renal failure.

Esophagus
the portion of the gastrointestinal tract that connects the throat (pharynx) to the stomach.

Ester
the product of a reaction between a carboxylic acid and an alcohol that involves the elimination of water. For example a cholesterol ester is the product of a reaction between a fatty acid and cholesterol.

Estrogen
a hormone that binds to estrogen receptors in the nuclei of cells and promotes the transcription of estrogen-responsive genes. Endogenous estrogens are steroid hormones produced by body. Exogenous estrogens are synthetic or natural compounds that have estrogenic activity (i.e., bind the estrogen receptor and promote estrogen-responsive gene transcription).

Etiology
the causes or origin of a disease.

Euglycemia
normal blood glucose concentrations.

Excitotoxicity
the toxicity that results from the continuous stimulation of nerve cells by neurotransmitters.

Excretion
the elimination of wastes from blood or tissues.

Executive function
a set of mental processes that helps connect past experience with present action. Executive functions include planning, organizing, strategizing, remembering details, and managing time and space.

Extracellular fluid (ECF)
the volume of body fluid excluding that in cells. ECF includes the fluid in blood vessels (plasma) and fluid between cells (interstitial fluid).

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Familial adenomatous polyposis
a hereditary syndrome characterized by the formation of many polyps in the colon and rectum, some of which may develop into colorectal cancer.

Fatty acid
an organic acid molecule consisting of a chain of carbon molecules and a carboxylic acid (-COOH) group. Fatty acids are found in fats, oils, and as components of a number of essential lipids, such as phospholipids and triglycerides. Fatty acids can be burned by the body for energy.

Femoral neck
a portion of the thighbone (femur). The femoral neck is found near the hip, at the base of the head of femur, which makes up the ball of the hip joint. Fractures of the femoral neck sometimes occur in individuals with osteoporosis.

Fetal macrosomia
a newborn of birth weight >4,000 grams (>8 pounds 13 ounces).

Fermentation
an anaerobic process that involves the breakdown of dietary components to yield energy.

Fibroblast
a cell that secretes extracellular matrix proteins, such as collagen, which give skin its structure. These cells are mostly found in the dermis and connective tissue.

Fibrocystic breast changes (FCC)
a benign (noncancerous) condition of the breasts, characterized by lumpiness and discomfort in one or both breasts.

First-pass metabolism
a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation due to action from the gastrointestinal tract and liver.

Food frequency questionnaire
a method of dietary assessment in which study participants are given a validated list of food and beverages and asked to report the frequency and portion size consumed over a given period of time.

Forced expiratory volume (FEV1)
the volume of air that can be expelled during the first second of a forced expiration. FEV1 is used to assess pulmonary (lung) function.

Fortification
the addition of nutrients to foods to prevent or correct a nutritional deficiency.

Fracture
a break in a bone or cartilage, often but not always the result of trauma.

Free radical
a very reactive atom or molecule typically possessing a single unpaired electron.

Fructosamine
describes a group of circulating proteins that have become irreversibly bound to glucose. Fructosamine assays provide information about blood glucose control two to three weeks prior to sample collection.

Fructose
a very sweet six-carbon sugar abundant in plants. Fructose is increasingly common in sweeteners such as high-fructose corn syrup.

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Gallbladder
a small sac adjacent to the liver. The gallbladder stores bile, which is secreted by the liver, and releases it into the small intestine through the common bile duct.

Gallstones
crystals formed by the precipitation of cholesterol or bilirubin in the gallbladder. Gallstones may be asymptomatic (without symptoms) or they may result in inflammation and infection of the gallbladder.

Gastric
pertaining to the stomach.

Gastric mucosa
a mucus membrane lining of the interior of the stomach that protects the underlying stomach tissue.

Gastritis
inflammation of the lining of the stomach.

Gastroesophageal reflux disease (GERD)
a condition in which stomach contents, including acid, back up (reflux) into the esophagus, causing inflammation and damage to the esophagus. GERD can lead to scarring of the esophagus and may increase the risk of cancer of the esophagus in some patients.

Gastrointestinal
referring to or affecting the digestive tract, which includes the mouth, pharynx (throat), esophagus, stomach, and intestines.

Gene
a region of DNA that controls a specific hereditary characteristic, usually corresponding to a single protein.

Gene expression
the process by which the information coded in genes (DNA) is converted to proteins and other cellular structures. Expressed genes include those that are transcribed to mRNA and translated to protein, as well as those that are only transcribed to RNA (e.g., ribosomal and transfer RNAs).

Genome
all of the genetic information (encoded in DNA) possessed by an organism.

Genotype
the genetic makeup of an individual cell or organism.

Gestation
the period of time between fertilization and birth. In humans, normal gestation is about 40 weeks.

Gingiva
the soft tissue lining the mouth (i.e., gums).

Gingivitis
inflammation of the gingiva.

Glomerulus (plural glomeruli)
a tuft of capillaries that makes up part of the filtering unit of the kidney (nephron).

Gluconeogenesis
the production of glucose from non-carbohydrate precursors, such as amino acids (the building blocks of proteins).

Glucose
a six-carbon sugar which plays a major role in the generation of energy for living organisms.

Glucose tolerance
the ability of the body to maintain normal glucose levels when challenged with a carbohydrate load (see impaired glucose tolerance).

Glucoside
a glycoside that contains glucose as its carbohydrate (sugar) moiety.

Glutamate
an excitatory neurotransmitter. Under certain circumstances glutamate may become toxic to neurons. Glutamate excitotoxicity appears to play a role in nerve cell death in some neurodegenerative disorders.

Glutathione
a tripeptide consisting of glutamate, cysteine, and glycine. Glutathione is an endogenous, intracellular antioxidant and is also required for some phase II biotransformation reactions.

Glycated hemoglobin
glucose-bound hemoglobin. A test for glycated hemoglobin measures the percentage of hemoglobin that is glucose bound. Since glucose remains bound to hemoglobin for the life of a red blood cell (~120 days), glycated hemoglobin values reflect blood glucose control over the past four months.

Glycemic index (GI)
an index of the blood glucose-raising potential of the carbohydrate in different foods. The GI is calculated as the area under the blood glucose curve after a test food is eaten, divided by the corresponding area after a control food (glucose or white bread) is eaten. The value is multiplied by 100 to represent a percentage of the control food.

Glycemic load (GL)
an index that simultaneously describes the blood glucose-raising potential of the carbohydrate in a food and the quantity of carbohydrate in a food. The GL of a food is calculated by multiplying the GI by the amount of carbohydrate in grams provided by a food and dividing the total by 100.

Glycogen
a large polymer (repeating units) of glucose molecules, used to store energy in cells, especially muscle and liver cells.

Glycolysis
the metabolic pathway in the cytosol that degrades glucose, producing energy in the form of ATP.

Glycoside
a compound containing a sugar molecule that can be cleaved by hydrolysis to a sugar and a nonsugar component (aglycone).

Goiter
enlargement of the thyroid gland. Goiter is one of the earliest and most visible signs of iodine deficiency. The thyroid enlarges in response to persistent stimulation by TSH. In mild iodine deficiency, this adaptive response may be enough to provide the body with sufficient thyroid hormone. However, more severe cases of iodine deficiency result in hypothyroidism. Thyroid enlargement may also be caused by factors other than iodine deficiency, especially in iodine sufficient countries, such as the US.

Goitrogen
a substance that induces goiter formation by interfering with thyroid hormone production or utilization.

Gout
a condition characterized by abnormally high blood levels of uric acid (urate). Urate crystals may form in joints, resulting in inflammation and pain. Urate crystals may also form in the kidney and urinary tract, resulting in kidney stones. The tendency to develop elevated blood uric acid levels and gout is often inherited.

Granular layer
the layer of the epidermis below the stratum corneum.

Gray matter
the darker-colored tissue in the central nervous system that contains mostly cell bodies and dendrites.

GTP
guanosine triphosphate. A high-energy molecule, required for a number of biochemical reactions, including nucleic acid and protein synthesis (formation).

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Haplotype
a set of DNA variations (polymorphisms) at adjacent locations on a chromosome; these DNA variations are inherited together.

Hartnup disease
a genetic disorder resulting in defective absorption of the amino acid, tryptophan.

HDL
high-density lipoproteins. HDL transport cholesterol from the tissues to the liver where it can be eliminated in bile. HDL-cholesterol is considered "good cholesterol," because higher blood levels of HDL-cholesterol are associated with lower risk of cardiovascular disease.

Hematocrit
the percentage of red blood cells in whole blood.

Hematology
the branch of medicine that studies the nature, function, disorders, and diseases of the blood, spleen, and lymph glands.

Heme
compounds of iron complexed in a characteristic ring structure known as a porphyrin ring.

Hemodialysis
the process of removing blood from an artery, removing waste products from the blood through dialysis, and returning blood to the body through a vein. Hemodialysis is used to treat end-stage renal failure.

Hemoglobin
the oxygen-carrying pigment in red blood cells.

Hemoglobin A1c
the main fraction of glycated (glucose-bound) hemoglobin. Since glucose remains bound to hemoglobin for the life of a red blood cell (~120 days), hemoglobin A1C values reflect blood glucose control over the past four months.

Hemolysis
rupture of red blood cells.

Hemolytic anemia
anemia resulting from hemolysis.

Hemorrhage
excessive or uncontrolled bleeding.

Hemorrhagic stroke
a stroke that occurs when a blood vessel ruptures and bleeds into the brain.

Hemorrhoids
dilated or enlarged veins of the anus and lower rectum.

Hemostasis
the arrest of bleeding.

Hepatic
relating to the liver.

Hepatic encephalopathy
a spectrum of neuropsychiatric signs or symptoms in individuals with acute or chronic liver disease.

Hepatitis
literally, inflammation of the liver. Hepatitis caused by a virus is known as viral hepatitis. Other causes of hepatitis include toxic chemicals and alcohol abuse.

Hepatocellular carcinoma
the most common type of primary liver cancer.

Hepatocyte
a parenchymal cell of the liver.

Hepatomegaly
an abnormally enlarged liver.

Hereditary hemochromatosis
a genetic disorder that results in iron overload despite normal dietary intake of iron.

Hereditary spherocytosis
a hereditary form of anemia characterized by abnormally shaped red blood cells which are spherical and abnormally fragile. The increased fragility of these red blood cells leads to hemolytic anemia (anemia caused by the rupture of red blood cells).

Heterodimer
a dimer or complex of two different molecules, usually proteins.

Heterogeneity
variability in study design and outcomes; the quality of being diverse and not comparable.

Heterozygous
possessing two different forms (alleles) of a specific gene.

Histology
the study of cells and tissues at the microscopic level.

Histone
protein that binds to DNA and packages it into compact structures to form nucleosomes.

HIV
human immunodeficiency virus; the virus that causes AIDS.

Homeostasis
a state of balance.

Homocysteine
a sulfur-containing amino acid, which is an intermediate in the metabolism of another sulfur-containing amino acid, methionine. Elevated homocysteine levels in the blood have been associated with increased risk of cardiovascular disease.

Homodimer
a dimer or complex of two of the same molecule, usually a protein.

Homologous
having the same appearance, structure, or evolutionary origin.

Homozygous
possessing two identical forms (alleles) of a specific gene.

Hormone
a chemical released by a gland or a tissue, which affects or regulates the activity of specific cells or organs. Complex bodily functions, such as growth and sexual development, are regulated by hormones.

Hot flushes
sensations of heat in the skin, particularly the face, neck, and chest; also known as hot flashes. Hot flushes are most often related to declining estrogen levels during the perimenopause (period surrounding menopause).

Human papilloma virus (HPV)
a group of viruses that may cause papillomas (growths or warts) on the skin or other parts of the body, including the genitals and the larynx (voice box). Infection with particular strains of HPV is associated with increased risk of cervical cancer.

Huntington's disease
an inherited degenerative disorder of the brain. Its symptoms include movement disorders and impaired cognitive function. Symptoms of Huntington's disease, previously known as Huntington's chorea, typically develop in the fourth decade of life and progressively deteriorate over time.

Hydrolysis
cleavage of a chemical bond by the addition of water. In hydrolysis reactions, a large compound may be broken down into smaller compounds when a molecule of water is added.

Hydrophilic
a molecule that has a high affinity for water and will readily dissolve in water.

Hydrophobic (lipophilic)
a molecule that repels water and thus will not dissolve in water.

Hydroxyapatite
a calcium phosphate salt. Hydroxyapatite is the main mineral component of bone and teeth and is what gives them their rigidity.

Hydroxylation
a chemical reaction involving the addition of a hydroxyl (-OH) group to a compound.

Hyperglycemia
an abnormally high blood glucose concentration; symptoms include increased thirst, increased urination, and general fatigue.

Hyperhomocysteinemia
abnormally elevated blood levels of homocysteine; associated with increased risk of cardiovascular disease.

Hyperhomocysteinuria
excessively high levels of plasma homocysteine.

Hyperkeratosis
irregular thickening of the stratum corneum due to increased number of corneocyte layers.

Hyperlipidemia
an abnormally high concentration of lipids in the blood.

Hypermetallation
refers to increased interactions between β-amyloid peptides and copper in Alzheimer's disease.

Hyperostosis
excessive growth of bone tissue.

Hyperparathyroidism
excess secretion of parathyroid hormone by the parathyroid glands resulting in the disturbance of calcium metabolism. Symptoms may include increased blood levels of calcium (hypercalcemia), decreased blood levels of phosphorus, loss of calcium from bone, and kidney stone formation.

Hyperplasia
excessive cell growth.

Hypertension
high blood pressure. According to the 2017 Clinical Practice Guidelines, hypertension is defined as a systolic blood pressure of 130 mm Hg or higher or a diastolic blood pressure of 80 mm Hg or higher.

Hyperthyroidism
an excess of thyroid hormone which may result from an overactive thyroid gland or nodule, or from taking too much thyroid hormone.

Hypertrophy
the enlargement of a tissue or organ due to an increase in the size of its cells.

Hypoglycemia
an abnormally low blood glucose concentration. Symptoms may include nausea, sweating, weakness, faintness, confusion hallucinations, headache, loss of consciousness, convulsions, or coma.

Hypoparathyroidism
a deficiency of parathyroid hormone, which may be characterized by low blood calcium levels (hypocalcemia).

Hypothalamus
an area at the base of the brain that regulates bodily functions, such as body temperature, hunger, and thirst.

Hypothesis
an educated guess or proposition that is advanced as a basis for further investigation. A hypothesis must be subjected to an experimental test to determine its validity.

Hypothyroidism
a deficiency of thyroid hormone that is normally made by the thyroid gland, located in the front of the neck.

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Idiopathic
of unknown cause.

Ileostomy
a surgically created connection between the ileum (part of the small intestine) and an opening in the abdominal wall (stoma) that allows for the evacuation of feces when a portion of the bowel has been removed.

Ileum
the third and final section of the small intestine.

Impaired glucose tolerance
a metabolic state between normal glucose regulation and overt diabetes. Impaired glucose tolerance is defined medically as a plasma glucose concentration between 140 and 199 mg/dL (7.8-11.0 mmol) two hours after the ingestion of 75 g of glucose during an oral glucose tolerance test.

Incontinence
inability to control the evacuation of urine or feces.

Induction
initiation of or increase in the expression of a gene in response to a physical or chemical stimulus (inducer).

Inflammation
a response to injury or infection, characterized by redness, heat, swelling, and pain. Physiologically, the inflammatory response involves a complex series of events, leading to the migration of white blood cells to the inflamed area.

Inflammatory bowel disease
a group of autoimmune diseases that affect the small and large intestines.

Insoluble
not dissolvable. With respect to bioavailability, certain substances form insoluble complexes that cannot be dissolved in digestive secretions, and therefore cannot be absorbed by the digestive tract.

Insulin
a peptide hormone secreted by the β-cells of the pancreas required for normal glucose metabolism.

Insulin resistance
diminished responsiveness to insulin.

Insulin sensitivity
the ability of tissues to respond to insulin.

Intermittent claudication
a condition characterized by leg pain or weakness on walking that diminishes or resolves with rest. It is usually associated with peripheral arterial disease.

International normalized ratio (INR)
the preferred method for reporting prothrombin time, a measure of coagulation status that may be used to evaluate the therapeutic efficacy of anticoagulants, such as warfarin. The INR is

a method for standardizing prothrombin time results so as to minimize variability between laboratories.

Intervention trial
an experimental study (usually a clinical trial) used to test the effect of a treatment or intervention on a health- or disease-related outcome.

Intestinal microbiota
the collection of microbial species that live specifically in the lower gastrointestinal tract (colon).

Intracellular fluid (ICF)
the volume of fluid inside cells.

Intraperitoneal (ip) injection
injection into the peritoneum.

Intravenous
within a vein.

Inverse association
a relationship between two variables in which they move in opposite directions.

In vitro
literally "in glass," referring to a test or research done in the test tube, outside a living organism.

In vivo
"inside a living organism." An in vivo assay evaluates a biological process occurring inside the body.

Ion
an atom or group of atoms that carries a positive or negative electric charge as a result of having lost or gained one or more electrons.

Ion channel
a protein embedded in a cell membrane that serves as a crossing point for the regulated transfer of an ion or a group of ions across the membrane.

Ischemia
a state of insufficient blood flow to a tissue.

Ischemic stroke
a stroke resulting from insufficient blood flow to an area of the brain, which may occur when a blood vessel supplying the brain becomes obstructed by a clot.

Isocaloric
having the same caloric density.

Isomer
one of two or more compounds that has the same number and kind of atoms but differs in the way the atoms are arranged.

Isotope
a different form of the same chemical element. Isotopes have the same number of protons but different numbers of neutrons.

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Jaundice
a yellowish staining of the skin and whites of the eyes due to increased bilirubin (a bile pigment) levels in the blood. Jaundice can be an indicator of red blood cells rupturing (hemolysis), or disease of the liver or gallbladder.

Keratinization
the process of cell differentiation of a keratinocyte through the different layers of the epidermis. At the end of keratinization, the cell is wider and flatter and attached to its neighboring cells by a variety of protein and lipid attachments.

Keratinocyte
primary cell type of the epidermis; these cells produce the structural protein keratin, which comprise the epidermal barrier.

Ketone bodies
any of three acidic chemicals (acetate, acetoacetate, and β-hydroxybutyrate). Ketone bodies may accumulate in the blood (ketosis) when the body has inadequate glucose to use for energy and must increase the use of fat for fuel. Ketone bodies are acidic, and very high levels in the blood are toxic and may result in ketoacidosis.

Kidney stones
solid masses resulting from the crystallization of minerals and other compounds found in urine. Common types of kidney stones include those composed of calcium oxalate, calcium phosphate and urate. Kidney stones may form in the kidneys, ureters, or urinary bladder.

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Langerhan cell
an antigen-presenting cell involved in epidermal immunity.

Laryngospasm
spasm that causes closure of the larynx, interfering with breathing.

Larynx
the area of the throat (pharynx) that contains the vocal cords.

LDL
low-density lipoprotein. LDLs transport cholesterol from the liver to the tissues of the body. Elevated serum LDL-cholesterol is associated with increased cardiovascular disease risk.

Left ventricular hypertrophy (LVH)
abnormal thickening of the wall of the left ventricle (lower chamber) of the heart muscle. The ventricles have muscular walls in order to pump blood from the heart through the arteries, but LVH occurs when the ventricle must pump against abnormally high volume or pressure loads. LVH may accompany congestive heart failure (CHF).

Legumes
members of the large family of plants known as leguminosae. In this context the term refers to the fruit or seeds of leguminous plants (e.g., peas and beans) that are used for food.

Lens
the transparent structure inside the eye that focuses light rays onto the retina (the nerve cells at the back of the eye).

Leptin
hormone secreted by adipose tissue that helps to regulate of food intake, body weight, and energy homeostasis.

Leptin resistance
resistance to the action of leptin.

Leukemia
an acute or chronic form of cancer that involves the blood-forming organs. Leukemia is characterized by an abnormal increase in the number of white blood cells in the tissues of the body, with or without a corresponding increase of those in the circulating blood, and is classified according to the type of white blood cell most prominently involved.

Leukocyte
white blood cell. Leukocytes are part of the immune system. Monocytes, lymphocytes, neutrophils, basophils, and eosinophils are different types of leukocytes.

Leukotriene
cell-signaling molecule involved in inflammation. Lipoxygenases catalyze the formation of leukotrienes from eicosanoids, such as arachidonic acid and eicosapentaenoic acid (EPA).

Ligand
a substance that binds to another molecule, forming a complex.

Lipid peroxidation
the process by which lipids are oxidatively modified; so named because lipid hydroperoxides are formed in the process.

Lipid
a chemical term for fat. Lipids found in the human body include fatty acids, phospholipids, and triglycerides.

Lipogenesis
the production of fatty acids.

Lipoic acid
a cofactor, essential for the oxidation of α-keto acids, such as pyruvate, in metabolism.

Lipolysis
the breakdown of lipids by hydrolysis.

Lipoprotein(a) [Lp(a)]
a lipoprotein particle in which the protein (apolipoprotein B-100) is chemically linked to another protein apolipoprotein(a). Increased blood levels of Lp(a) are associated with an increased risk of cardiovascular disease.

Lipoprotein
particle composed of lipids and protein that allows for the transport of lipids through the bloodstream. A lipoprotein particle is composed of an outer layer of phospholipids, which renders it soluble in water, and a hydrophobic core that contains triglycerides and cholesterol esters. Different types of lipoproteins are distinguished by their surface proteins (apoproteins), their size, and the types and amounts of lipids they contain.

Lumbar spine
the portion of the spine between the chest (thorax) and the pelvis. It is commonly referred to as the small of the back.

Lumen
the channel within a tube such as a blood vessel or the intestine.

Lupus
see systemic lupus erythematosus (SLE).

Lymphocyte
leukocyte (white blood cells) that plays important roles in the immune system. T lymphocytes (T cells) differentiate into cells that can kill infected cells or activate other cells in the immune system. B lymphocytes (B cells) differentiate into cells that produce antibodies.

Lysosome
a cellular organelle containing hydrolytic enzymes specialized for breaking down cellular debris. Lysosomal enzymes are separated from the rest of the cell by a lysosomal membrane and function optimally at an acidic pH.

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Macrocytic anemia
low red blood cell count, characterized by the presence in the blood of larger than normal red blood cells.

Macronutrient
nutrients required in relatively large amounts; macronutrients include carbohydrates, proteins, and lipids.

Macrophage
white blood cell that engulfs and degrades pathogens (bacteria) and cellular debris. Macrophages are activated or transformed monocytes.

Macula
a small area of the retina where vision is the sharpest. The macula is located in the center of the retina and provides central vision.

Magnetic Resonance Imaging (MRI)
a special imaging technique that uses a powerful magnet and a computer to provide clear images of soft tissues. Tissues that are well-visualized using MRI include the brain and spinal cord, abdomen, and joints.

Malabsorption syndrome
a disease or condition that results in poor absorption of nutrients from food.

Malaria
an infectious disease caused by parasitic microorganisms called plasmodia. Malaria can be spread among humans through the sting of certain types of mosquitos (Anopheles) or by a contaminated needle or transfusion. Malaria is a major health problem in the tropics and subtropics, affecting over 200 million people worldwide.

Malignant
cancerous.

Matrix metalloproteinase (MMP)
a proteolytic enzyme that degrades extracellular matrix proteins, such as collagen and elastin.

M cells
membranous or microfold cells; specialized cells in the intestinal epithelium that internalize pathogenic microorganisms to the gut-associated lymphoid tissue.

Measurement error
the difference between a measured value and its true value.

Megaloblastic anemia
low red blood cell count, characterized by the presence in the blood of large, immature, nucleated cells (megaloblasts) that are forerunners of red blood cells. Red blood cells, when mature, have no nucleus.

Melanin
a dark brown pigment found in the skin.

Melanocyte
a pigment-containing cell of the epidermis. The pigment, melanin, absorbs ultraviolet light and protects the skin from damage. Unlike keratinocytes, melanocytes are not shed over time.

Membrane potential
the electrical potential difference across a membrane. The membrane potential is a result of the concentration differences between potassium and sodium across cell membranes, which are maintained by ion pumps. A large proportion of the body's resting energy expenditure is devoted to maintaining the membrane potential, which is critical for nerve impulse transmission, muscle contraction, heart function, and the transport of nutrients and metabolites in and out of cells.

Menarche
the first occurrence of menstruation.

Mendelian randomization study
genetic study conducted to assess whether genetic determinants of a risk factor are related to clinical outcomes.

Menstruation
the cyclic loss of blood by a woman from her uterus (womb) when she is not pregnant. Menstruation generally occurs every four weeks after a woman has reached sexual maturity and prior to menopause.

Meta-analysis
a statistical technique used to combine the results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or exposure on a defined outcome.

Metabolic syndrome
a combination of medical conditions that places one at risk for cardiovascular disease and type 2 diabetes. (Metabolic syndrome is also called metabolic syndrome X, syndrome X, and insulin resistance syndrome.) Diagnostic criteria include the presence of three or more of the following conditions:

- Abdominal obesity (waist circumference: ≥40 inches [102 cm] for men, ≥35 inches [88 cm] for women)
- Elevated triglycerides (≥150 mg/dL or on drug treatment for elevated triglycerides)
- High blood pressure (≥130 mm Hg for systolic blood pressure and/or ≥85 mm Hg for diastolic blood pressure, or taking anti-hypertensive drugs)
- Glucose intolerance/insulin resistance (fasting blood glucose ≥100 mg/dL, or on drug treatment for elevated glucose)
- Decreased HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women, or on drug treatment for low HDL cholesterol)

Metabolism
the sum of the processes (reactions) by which a substance is assimilated and incorporated into the body or detoxified and excreted from the body.

Metabolite
a compound derived from the metabolism of another compound is said to be a metabolite of that compound.

Metastasize
to spread from one part of the body to another. Cancer is said to metastasize when it spreads from the primary site of origin to a distant anatomical site.

Methionine
a sulfur containing amino acid, required for protein synthesis and other vital metabolic processes. It can be obtained through the diet in protein or synthesized from homocysteine.

Methylation
a biochemical reaction resulting in the addition of a methyl group (-CH$_3$) to another molecule.

Micelle
an aggregate or cluster of amphipathic molecules in water. Amphipathic molecules have a polar or hydrophilic end and a nonpolar or hydrophobic end. In micelles, amphipathic molecules orient with their hydrophobic ends in the interior and their hydrophilic ends on the exterior surface, exposed to water.

Micronutrient
a nutrient required by the body in small amounts, such as a vitamin or a mineral.

MicroRNA
small non-coding RNA involved in the regulation of gene expression.

Microtia
underdevelopment of the external ear.

Migraine headache
a type of headache thought to be related to abnormal sensitivity of blood vessels (arteries) in the brain to various triggers resulting in rapid changes in the artery size due to spasm (constriction). Other arteries in the brain and scalp then open (dilate), and throbbing pain is perceived in the head. The tendency toward migraine appears to involve serotonin, a neurotransmitter that can trigger the release of vasoactive substances in the blood vessels.

Mineral
nutritionally significant element. Elements are composed of only one kind of atom. Minerals are inorganic, i.e., they do not contain carbon as do vitamins and other organic compounds.

Minimal Erythemal Dose (MED)
the lowest dose of ultraviolet radiation (UVR) that will produce a detectable erythema 24 hours after UVR exposure.

Mitochondria
energy-producing structures within cells. Mitochondria possess two sets of membranes: a smooth continuous outer membrane and an inner membrane arranged in folds. Among other critical functions, mitochondria convert nutrients into energy via the electron transport chain.

Mitosis
the process of cell division.

mm Hg
millimeters of mercury. The unit of measure for blood pressure.

Moiety
a portion of something, such as a functional group of a molecule.

Mole
the fundamental unit for measuring chemical compounds (abbreviated mol). One mole equals the molecular weight of a compound in grams. The number of molecules in a mole is equal to 6.02 x 10^{23} (Avogadro's number).

Molecular chaperone
a class of proteins that facilitates in the folding and assembly of other proteins.

Monocyte
white blood cell that is the precursor to a macrophage.

Monomer
a molecule that can be chemically bound as a unit of a polymer.

Monotherapy
the use of a single medication to treat a condition.

Monounsaturated fatty acid
a fatty acid with only one double bond between carbon atoms.

mRNA
short for messenger ribonucleic acid (RNA). These molecules are the ‘message' that encodes the proteins produced in cells. Increases or decreases in mRNA levels will alter protein production in cells.

Mucin
a glycoprotein that lubricates and protects body surfaces.

Mucocutaneous
relating to the mucous membranes of the skin.

Multifactorial
refers to diseases or conditions that are the result of interactions between multiple genetic and environmental factors.

Multiple sclerosis (MS)
an autoimmune disorder in which the myelin sheaths of nerves in the brain and spinal cord are damaged, resulting in progressive neurological symptoms.

Mutagen
an agent that can induce mutation.

Mutation
a change in a gene; in other words, a change in the sequence of base-pairs in the DNA that makes up a gene. Mutations in a gene may or may not result in an altered gene product.

Myelin
the fatty substance that covers myelinated nerves. Myelin is a layered tissue surrounding the axons or nerve fibers. This sheath acts as a conduit in an electrical system, allowing rapid and efficient transmission of nerve impulses.

Myelination
the formation of the myelin sheath around a nerve fiber.

Myeloid
derived from bone marrow.

Myocardial infarction (MI)
death (necrosis) of heart muscle tissue due to an interruption in its blood supply. Commonly known as a heart attack, an MI usually results from the obstruction of a coronary artery by a clot in people who have coronary atherosclerosis.

Myocardial stunning
a temporary dysfunction of the cardiac myocardium (contractile abormality) following ischemia and reperfusion.

Myocarditis
an inflammation of the heart muscle.

Myocyte
muscle cell.

Myoglobin
a heme-containing pigment in muscle cells that binds and stores oxygen.

Myopathy
any disease of muscle.

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Natural killer (NK) cells
cytotoxic lymphocytes important for the innate immune response that kills pathogens. NK cells also have important roles in killing cancer cells.

Necrosis
unprogrammed cell death, in which cells break open and release their contents, promoting inflammation. Necrotic cell death may be the result of injury, infection, or infarction.

Neoplasm
a term referring to a rapid and abnormal growth of tissue. Neoplasms can be benign or malignant.

Nephropathy
kidney damage or disease.

Nerve impulse
the electrochemical signal transmitted in the cell membrane of a neuron or muscle cell. Also called action potential.

Nested case-control study
a case-control study within a cohort study; cases of a disease that occur in a defined cohort are identified, and a specified number of matched controls is then selected from the larger cohort for comparison.

Neural Tube Defect (NTD)
a birth defect caused by abnormal development of the neural tube, the structure which gives rise to the central nervous system. Neural tube defects include anencephaly and spina bifida.

Neurodegenerative disease
disease resulting from the degeneration or deterioration of nerve cells (neurons). Alzheimer's disease and Parkinson's disease are neurodegenerative diseases.

Neurogenesis
the formation and development of nerves, nerve tissue, or the nervous system.

Neurologic
or neurological; involving nerves or the nervous system (brain, spinal cord, and all sensory and motor nerves).

Neuron
cell of the nervous system that conducts nerve impulses. Also called nerve cell.

Neuropathy
nerve damage or disease.

Neurotoxic
toxic or damaging to nervous tissue (brain and peripheral nerves).

Neurotransmitter
a chemical that is released from a nerve cell and results in the transmission of an impulse to another nerve cell or organ (e.g., a muscle). Acetylcholine, dopamine, norepinephrine, and serotonin are neurotransmitters.

Neutrophil
white blood cell that internalizes and destroys pathogens, such as bacteria. Neutrophils are also called polymorphonuclear leukocytes because they are white blood cells with multi-lobed nuclei.

NIH
US National Institutes of Health. Administered under the US Department of Health and Human Services (HHS), the NIH are more than 20 separate institutes and centers devoted to medical research.

Nitric oxide
a gaseous signaling molecule synthesized from the amino acid arginine by enzymes called nitric oxide synthases. In the vascular endothelium, nitric oxide promotes arterial vasodilation.

Normotensive
having normal blood pressure, i.e., a systolic blood pressure <120 mm Hg and a diastolic blood pressure <80 mm Hg.

Nucleic acid
DNA (deoxyribonucleic acid) and RNA (ribonucleic acid); long polymer of nucleotides.

Nucleosome
repeating unit of chromatin that consists of DNA that is coiled around histones.

Nucleoside
a compound composed of a nitrogen-containing base (adenine, guanine, cytosine, uracil, or thymine) linked to either ribose or deoxyribose.

Nucleotide
subunit of nucleic acids. Nucleotides are composed of a nitrogen-containing base (adenine, guanine, cytosine, uracil, or thymine), a five-carbon sugar (ribose or deoxyribose), and one or more phosphate groups.

Nucleus
a membrane-bound cellular organelle, which contains DNA organized into chromosomes.

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Obesity
a condition of increased body fat; defined as a body mass index (BMI) ≥30 for adults.

Observational study
a study in which no experimental intervention or treatment is applied. Participants are simply observed over time.

Ocular
relating to the eye.

Odds ratio (OR)
a measure of association comparing the odds of an outcome in the exposed group to the odds of an outcome in the non-exposed (control) group. The OR is an approximation of the relative risk.

Omega-3 index
the amount of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) in red blood cell membranes expressed as the percent of total red blood cell membrane fatty acids.

Oncology
the field of medicine dealing with cancer and tumors.

One-carbon unit
a biochemical term for functional groups containing only one carbon in addition to other atoms. One-carbon units transferred by folate coenzymes include methyl (-CH$_3$), methylene (-CH$_2$-), formyl (-CH=O), formimino (-CH=NH), and methenyl (-CH=). Many biosynthetic reactions involve the addition of a one-carbon unit to a precursor molecule.

Open-label trial
a clinical trial in which the investigators and participants are aware of the treatment (i.e., it is not double-blind).

Optimum health
in addition to freedom from disease, the ability of an individual to function physically and mentally at his or her best.

Oral (po) administration
administration of a substance by mouth.

Organelle
a specialized component of a cell, such as the mitochondrian or lysosome, so named because they are analogous to organs.

Organic
refers to carbon-containing compounds, generally synthesized by living organisms.

Oropharynx
a term used to describe the mouth and throat.

Osteoarthritis
a degenerative joint condition that is characterized by the breakdown of articular cartilage (cartilage within the joint).

Osteoblast
bone cell that is responsible for the formation of new bone mineral in the bone remodeling process.

Osteoclast
bone cell that is responsible for the breakdown or resorption of bone in the bone remodeling process.

Osteocyte
a type of bone cell formed from an osteoblast once it becomes embedded deep within the organic matrix.

Osteomalacia
a disease of adults that is characterized by softening of the bones due to loss of bone mineral. Osteomalacia is characteristic of vitamin D deficiency in adults, while children with vitamin D deficiency suffer from rickets.

Osteonecrosis
death of bone tissue.

Osteopenia
a condition of low bone mass clinically defined as having a T-score one to 2.5 standard deviations (SD) below that of the average young adult (30 years of age) female.

Osteoporosis
a condition of increased bone fragility and susceptibility to bone fracture due to a loss of bone mineral density (BMD)

Overnutrition
a form of malnutrition where nutrients are supplied in excess of the body's needs.

Oxidant
reactive oxygen species.

Oxidation
a chemical reaction that removes electrons from an atom or molecule.

Oxidative damage
damage to cells caused by reactive oxygen species.

Oxidative stress
a condition, in which the effects of pro-oxidants (e.g., free radicals, reactive oxygen and reactive nitrogen species) exceed the ability of antioxidant systems to neutralize them.

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Pancreas
a small organ located behind the stomach and connected to the duodenum (part of the small intestine). The pancreas synthesizes enzymes that help digest food in the small intestine and hormones, including insulin, that regulate blood glucose levels.

Papillary dermis
the uppermost layer of the dermis.

Parathyroid glands
glands located behind the thyroid gland in the neck. The parathyroid glands secrete a hormone called parathyroid thormone (PTH) that is critical to calcium and phosphorus metabolism.

Parenteral nutrition
intravenous administration of nutrition.

Parkinson's disease
a disease of the nervous system caused by degeneration of a part of the brain called the basal ganglia, as well as by low production of the neurotransmitter dopamine. Symptoms include muscle rigidity, tremors, and slow voluntary movement.

Pathogen
disease-causing agents, such as viruses or bacteria.

Pathogenesis
the biological mechanisms underlying the development of a disease.

Pathology
the branch of medicine that studies the causes and effects of disease.

Peptic ulcer disease
a disease characterized by ulcers or breakdown of the inner lining of the stomach or duodenum. Common risk factors for peptic ulcer disease include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and infection with *Helicobacter pylori*.

Peptide
a chain of amino acids. A protein is made up of one or more peptides.

Peptide hormone
a hormone that is a protein, as opposed to a steroid hormone, which is made from cholesterol. Insulin is an example of a peptide hormone.

Percutaneous
through the skin.

Percutaneous transluminal coronary angioplasty (PTCA)
a nonsurgical technique, in which a balloon catheter is inserted into a peripheral artery and passed into an occluded coronary artery, where the balloon is inflated to dilate the artery.

Perinatal
the period of time just before and after birth (varyingly defined as the time period starting between 20 to 28 weeks' gestation and ending one to four weeks after birth).

Periodontium
the tissues and gingiva surrounding the teeth.

Peripheral arterial disease
atherosclerosis of the arteries of the extremities.

Peripheral neuropathy
a disease or degenerative state affecting the nerves of the extremities (arms and legs). Symptoms may include numbness, pain, and muscle weakness.

Peripheral vascular disease
atherosclerosis of the vessels of the extremities, which may result in insufficient blood flow or pain in the affected limb, particularly during exercise.

Peritoneal dialysis
a procedure in which a special dialysis solution is introduced through a tube in the peritoneum. The dialysis solution pulls wastes and extra fluid from the body when the dialysis solution is drained through the same tube. The most common form is called continuous ambulatory peritoneal dialysis and can be performed at home without a machine.

Peritoneum
a membrane that lines the walls of the abdominal cavity.

Pernicious anemia
the end stage of an autoimmune inflammation of the stomach, resulting in destruction of stomach cells by one's own antibodies. Progressive destruction of the cells that line the stomach cause decreased secretion of acid and enzymes required to release food bound vitamin B$_{12}$. Antibodies to intrinsic factor (IF) bind to IF preventing formation of the IF-B$_{12}$ complex, further inhibiting vitamin B$_{12}$ absorption.

PET scan
positron emission tomography scan. A diagnostic imaging technique that uses a sophisticated camera and computer to produce images of how a person's body is functioning. A PET scan shows the difference between healthy and abnormally functioning tissues.

pH
a measure of acidity or alkalinity.

Phagocyte
a specialized cell, such as a macrophage, that engulfs and digests invading microorganisms through the process of phagocytosis.

Phagocytosis
process by which phagocytes engulf and digest invading microorganisms and foreign particles.

Phagosome
an intracellular vesicle containing the foreign material engulfed by the phagocyte.

Pharmacokinetics
the study of the absorption, distribution, metabolism, and elimination of drugs and other compounds.

Pharmacological dose
the dose or intake level of a nutrient many times the level associated with the prevention of deficiency or the maintenance of health. A pharmacologic dose is generally associated with the treatment of a disease state and considered to be a dose at least 10 times greater than that needed to prevent deficiency.

Phase I clinical trial
a clinical trial in a small group of people aimed at determining bioavailability, optimal dose, safety, and early evidence of the efficacy of a new therapy.

Phase II clinical trial
a clinical trial designed to investigate the effectiveness of a new therapy in larger numbers of people and to further evaluate short-term side effects and safety of the new therapy.

Phase III clinical trial
once a drug or treatment has been shown to be efficacious and safe in phase I and II clinical trials, a large, phase III clinical trial must be conducted before the drug or treatment receives formal FDA approval.

Phenolic compounds
a class of chemical compounds consisting of a hydroxyl functional group (-OH) attached to an aromatic hydrocarbon group. An aromatic hydrocarbon has a ring structure like that of benzene. Polyphenolic compounds contain more than one phenolic group.

Phenylketonuria (PKU)
an inherited disorder resulting in the inability to process the amino acid, phenylananine. If not treated, the disorder may result in mental retardation. Treatment is a diet low in phenylalanine. Newborns are screened for PKU, in order to determine the need for treatment before brain damage occurs.

Phlebotomy
the removal of blood from a vein. Phlebotomy may be used to obtain blood for diagnostic tests or to treat certain conditions, for example, iron overload in hemochromatosis.

Phospholipid
lipid in which phosphoric acid, as well as fatty acids, are attached to a glycerol backbone. Phospholipids are important structural components of cell membranes.

Phosphorylation
the creation of a phosphate derivative of an organic molecule. This is usually achieved by transferring a phosphate group (-PO$_4$) from ATP to another molecule.

Photodamage
skin damage induced by ultraviolet (UV) light that is absorbed in an uncontrolled manner by molecules in the body. Depending on the dose, UV light can cause cell death and an inflammatory response.

Physiologic dose
the dose or intake level of a nutrient associated with the prevention of deficiency or the maintenance of health. A physiologic dose of a nutrient is not generally greater than that which could be achieved through a conscientious diet, as opposed to the use of supplements.

Phytochemical
biologically active, non-nutrient compound synthesized by plants.

Phytoestrogen
a plant-derived compound with estrogenic activity.

Pigment
a compound that gives a plant or animal cell color by the selective absorption of different wavelengths of light.

Pilosebaceous unit
hair follicles in the skin that are associated with a sebaceous gland.

Pilot study
a preliminary study conducted on a small scale in order to prepare for a larger study.

Pituitary gland
a small oval gland located at the base of the brain that secretes hormones regulating growth and metabolism. The pituitary gland is divided into two separate glands, the anterior and posterior pituitary glands, which each secrete different hormones.

Placebo
an inert treatment that is given to a control group while the experimental group is given the active treatment. Placebo-controlled studies are conducted to make sure that the results are due to the experimental treatment, rather than another factor associated with participating in the study.

Placenta
the organ that connects the fetus to the pregnant woman's uterus, allowing for the exchange of oxygen, carbon dioxide, nutrients, and waste between woman and fetus.

Placental abruption
premature separation of the placenta from the wall of the uterus. Abruption is a potentially serious problem both for the woman and fetus.

Plasma
whole blood without blood cells; that is, red blood cells and white blood cells have been removed. Plasma is separated from blood cells using a centrifuge. Unlike serum, plasma retains clotting factors because it is obtained from blood that is not allowed to clot.

Platelet
irregularly shaped cell fragments that assist in blood clotting.

Pneumonia
a disease of the lungs characterized by inflammation and accumulation of fluid in the lungs. Pneumonia may be caused by infectious agents (e.g., viruses or bacteria) or by inhalation of certain irritants.

Polymer
a large molecule formed by combining many similar smaller molecules (monomers) in a regular pattern.

Polymorphism
a nucleotide difference (variant) in the DNA sequence of a gene. Most polymorphisms are harmless and are part of normal human genetic variation, but some polymorphisms affect the function of the gene product (protein).

Polyp
a benign (non-cancerous) mass of tissue that forms on the inside of a hollow organ, such as the colon.

Polyphenolic compound
a phenolic compound that contains more than one phenolic group.

Polyunsaturated fatty acid
a fatty acid with more than one double bond between carbons.

Postprandial
after eating or after a meal.

Prebiotic
a non-digestible, fermentabl fiber that influences the composition of the intestinal microbiota.

Precursor
a molecule which is an ingredient, reactant, or intermediate in a synthetic pathway for a particular product.

Preeclampsia
a condition characterized by a sharp rise in blood pressure during the third trimester of pregnancy. High blood pressure may be accompanied by edema (swelling) and proteinuria (protein in the urine). In some cases, untreated preeclampsia can progress to eclampsia, a life-threatening situation for the woman and child.

Prevalence
the proportion of a population with a specific disease or condition at a given point in time.

Probiotic
live cultures of microorganisms that, when administered in sufficient amounts, benefits the overall health of the host.

Procarcinogen
a carcinogen precursor that must be modified or metabolized to become an active carcinogen.

Prodrug
a precursor to a drug, i.e., an inactive compound that can be metabolized in the body to produc an active drug.

Prognosis
predicted outcome based on the course of a disease.

Proliferation
the reproduction or multiplication of cells.

Promoter
DNA sequence to which RNA polymerase binds to initiate transcription.

Pro-oxidant
an atom or molecule that promotes oxidation of another atom or molecule by accepting electrons. Examples of pro-oxidants include free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS).

Prophylaxis
prevention, often refers to a treatment used to prevent a disease.

Prospective cohort study
an observational study in which a group of people—known as a cohort—are interviewed or tested for risk factors (e.g., nutrient intake), and then followed up at subsequent times to determine their status with respect to a disease or health outcome.

Prostaglandin
cell-signaling molecule that is involved in inflammation. Cyclooxygenases catalyze the formation of prostaglandins from eicosanoids, such as arachidonic acid and eicosapentaenoic acid (EPA).

Prostate
a gland in men, located at the base of the bladder and surrounds the urethra. The prostate produces fluid that forms part of semen. If the prostate becomes enlarged it may exert pressure on the urethra and cause urinary symptoms. Prostate cancer is one of the most common types of cancer in men.

Prostate-specific antigen (PSA)
a compound normally secreted by the prostate that can be measured in the blood. If prostate cancer is developing, the prostate secretes larger amounts of PSA. Blood tests for PSA are used to screen for prostate cancer and to follow up on prostate cancer treatment.

Protein
a complex organic molecule composed of amino acids in a specific order. The order is determined by the sequence of nucleic acids in a gene coding for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs, and each protein has unique functions.

Proteoglycan
a large compound comprised of protein and polysaccharide units known as glycosaminoglycans (GAGs). GAGs are polymers of sugars and amino sugars, such as glucosamine or galactosamine. Proteoglycans are integral components of structural tissues like bone and cartilage.

Proteolysis
the breakdown of proteins by protease enzymes.

Proton
an elementary particle identical to the nucleus of a hydrogen atom, which along with neutrons, is a constituent of all other atomic nuclei. A proton carries a positive charge equal and opposite to that of an electron.

Pruritus
itching.

Psoriasis
a chronic skin condition often resulting in a red, scaly rash located over the surfaces of the elbows, knees, scalp, and around or in the ears, navel, genitals, or buttocks. Approximately 10-15% of patients with psoriasis develop joint inflammation (psoriatic arthritis). Psoriasis is thought to be an autoimmune condition.

Pyruvate kinase deficiency
a hereditary deficiency of the enzyme pyruvate kinase. Pyruvate kinase deficiency results in hemolytic anemia.

Quartile
one-fourth of a sample or population.

Quintile
one-fifth of a sample or population.

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Racemic mixture
a mixture of equal amounts of isomers that are mirror images of each other (enantiomers).

Radiation therapy
the local use of radiation to destroy cancer cells or stop them from dividing and growing.

Randomized controlled trial (RCT)
a clinical trial with at least one active treatment group and a control (placebo) group. In RCTs, participants are chosen for the experimental and control groups at random and are not told whether they are receiving the active or placebo treatment until the end of the study. This type of study design can provide evidence of causality.

Randomized design
an experiment in which participants are chosen for the experimental and control groups at random, in order to reduce bias caused by self-selection into experimental and control groups. This type of study design can provide evidence of causality.

RDA
recommended dietary allowance. Established by the Food and Nutrition Board of the US Institute of Medicine, the RDA is the average daily dietary intake level of a nutrient sufficient to meet the requirements of nearly all healthy individuals in a specific life stage and gender group.

Reactive nitrogen species (RNS)
highly reactive chemicals, containing nitrogen, that react easily with other molecules, resulting in potentially damaging modifications.

Reactive oxygen species (ROS)
highly reactive chemicals, containing oxygen, that react easily with other molecules, resulting in potentially damaging modifications.

Recall bias
a type of measurement error caused by inaccuracies in the recollection of study participants regarding past behaviors and experiences.

Receptor
a specialized molecule inside or on the surface of a cell that binds a specific chemical (ligand). Ligand binding usually results in a change in activity within the cell.

Recessive trait
a trait that is expressed only when two copies of the gene responsible for the trait are present.

Rectum
the last portion of the large intestine, connecting the sigmoid colon (above) to the anus (below). The rectum stores stool until it is evacuated from the body.

Redox reaction
another term for an oxidation-reduction reaction. A redox reaction is any reaction in which electrons are removed from one molecule or atom and transferred to another molecule or atom. In such a reaction one substance is oxidized (loses electrons) while the other is reduced (gains electrons).

Reducing equivalent
an amount of a reducing compound that donates the equivalent of one mole of electrons or hydrogen ions in a redox reaction.

Reduction
a chemical reaction in which a molecule or atom gains electrons.

Reepithelialization
a rapid process of cell growth by which the epidermis repairs itself after a wounding event. The goal of reepithelialization is to re-establish a functional barrier that protects underlying cells from environmental exposures.

Relative Risk (RR)
the probability of a negative outcome in the exposed group divided by the probability of the negative outcome in the non-exposed (control) group.

Renal
refers to the kidneys.

Replete
in nutrition, having fulfilled nutrient requirements.

Residual confounding
results when investigators fail to completely control for confounders by adjustment in statistical analyses.

Residue
a single unit within a polymer, such as an amino acid within a protein.

Resorption
the process of breaking down or assimilating something. With respect to bone, resorption refers to the breakdown of bone by osteoclasts, resulting in the release of calcium and phosphate (bone mineral) into the blood.

Response element
a sequence of nucleotides in a gene that can be bound by a protein. Proteins that bind to response elements in genes are sometimes called transcription factors or binding proteins. Binding of a transcription factor to a response element regulates the production of specific proteins by inhibiting or enhancing the transcription of genes that encode those proteins.

Restenosis
with respect to the coronary arteries, restenosis refers to the reocclusion of a coronary artery after it has been dilated using coronary angioplasty.

Retina
the nerve layer that lines the back of the eye. In the retina, images created by light are converted to nerve impulses, which are transmitted to the brain via the optic nerve.

Retrospective study
an epidemiological study that looks back in time. A retrospective study begins after the exposure and the disease have occurred. Most case-control studies are retrospective.

Reverse causation
a concept that refers to the counterintuitive direction in a cause-and-effect association, when it is the effect that influences the cause; E.g., if low vitamin D status is common in people affected by multiple sclerosis (MS), it might be because those with MS spend less time outdoors and therefore synthesize less vitamin D in their skin (reverse causation), rather than because poor vitamin D status increases the risk of MS.

Rheumatoid arthritis
a chronic autoimmune disease characterized by inflammation of the synovial lining of the joints. Rheumatoid arthritis may also affect other organs of the body, including the skin, eyes, lungs, and heart.

Ribonucleotide
a molecule consisting of a five-carbon sugar (ribose), a nitrogen-containing base, and one or more phosphate groups.

Rickets
often the result of vitamin D deficiency. Rickets affects children while their bones are still growing. It is characterized by soft and deformed bones and is the result of an impaired incorporation of calcium and phosphate into the skeleton.

Risk
the probability of a negative outcome occurring.

RNA
ribonucleic acid; a single-stranded nucleic acid composed of many nucleotides. The nucleotides in RNA are composed of a nitrogen-containing base (adenine, guanine, cytosine, or uracil), a five-carbon sugar (ribose) and a phosphate group. RNA functions in the translation of the genetic information encoded in DNA to proteins.

Rumen
the first part of the stomach of a ruminant.

Ruminant
an animal that chews cud. Ruminant animals include cattle, goats, sheep, and deer.

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Satiety
a state of fullness.

Saturated fatty acid
a fatty acid with no double bonds between carbon atoms.

Scavenge (free radicals)
to combine readily with free radicals, preventing them from reacting with other molecules.

Schizophrenia
a debilitating brain disorder that affects about 1% of the world's population. Symptoms may include hallucinations, delusions, thought disorders, disorders of movement, cognitive deficits, lack of emotional expression, or impaired ability to speak, plan, and interact with others. Although its cause is not known, schizophrenia is thought to result from a combination of genetic and environmental factors.

Scurvy
a disorder caused by lack of vitamin C. Symptoms include anemia, bleeding gums, tooth loss, joint pain, and fatigue. Scurvy is treated by supplying foods high in vitamin C, as well as with vitamin C supplements.

Sebaceous gland
gland found at the base of hair follicles that secretes sebum.

Sebocyte
a sebum-producing cell in the skin.

Sebum
a waxy/oily substance secreted by mammals that coats the outer layer of the skin.

Seizure
uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms.

Senile plaque
plaques made by deposits of β-amyloid peptides in Alzheimer's disease.

Serotonin
5-hydroxytryptamine. Serotonin is a neurotransmitter that may also function as a vasoconstrictor (substance that causes blood vessels to narrow).

Serum
whole blood without clotting factors. Serum is separated from blood cells using a centrifuge. Unlike plasma, serum lacks clotting factors because it is obtained from blood that has been allowed to clot.

Short bowel syndrome
a malabsorption syndrome resulting from the surgical removal of an extensive portion of the small intestine.

Sickle cell anemia
a hereditary disease in which a mutation in the gene for one of the proteins that comprises hemoglobin results in the formation of defective hemoglobin molecules known as hemoglobin S. Individuals who are homozygous for this mutation (possess two genes for hemoglobin S) have red blood cells that change from the normal discoid shape to a sickle shape when the oxygen supply is low. These sickle-shaped cells are easily trapped in capillaries and damaged, resulting in severe anemia. Individuals who are heterozygous for the mutation (possess one gene for hemoglobin S and one normal hemoglobin gene) have increased resistance to malaria.

Sideroblastic anemia
a group of anemias that are all characterized by the accumulation of iron deposits in the mitochondria of immature red blood cells. These abnormal red blood cells do not mature normally, and many are destroyed in the bone marrow before reaching the circulation. Sideroblastic anemias can be hereditary, idiopathic (unknown cause), or caused by such diverse factors as certain drugs, alcohol, or copper deficiency.

Signal transduction pathway
a cascade of events that allows a signal outside a cell to result in a functional change inside the cell. Signal transduction pathways play important roles in regulating numerous cellular functions in response to changes in a cell's environment.

Sleep apnea
a sleep disorder characterized by repeated cessation of breathing.

Small intestine
the part of the digestive tract that extends from the stomach to the large intestine. The small intestine includes the duodenum (closest to the stomach), the jejunum, and the ileum (closest to the large intestine).

Soluble
capable of being dissolved.

Sorbitol
the polyol (sugar alcohol) corresponding to glucose.

Spermatogenesis
the formation and development of mature spermatozoa.

Spermatozoon
the mature male reproductive cell.

Spina bifida
a birth defect, also known as a neural tube defect, resulting from failure of the lower end of the neural tube to close during embryonic development. Spina bifida, the most common cause of infantile paralysis, is characterized by a lack of protection of the spinal cord by its membranes and vertebral bones.

Spongiosis
intercellular edema in the epidermis.

Sprue
also known as celiac sprue and celiac disease, it is an inherited disease in which the intestinal lining is inflamed in response to the ingestion of a protein known as gluten. Treatment of celiac disease involves the avoidance of gluten, which is present in many grains, including wheat, rye, oats, and barley. Inflammation and atrophy of the lining of the small intestine leads to impaired nutrient absorption.

Statin
a drug that inhibits the enzyme, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, thus decreasing endogenous synthesis of cholesterol and lowering blood cholesterol concentrations.

Status
the state of nutrition of an individual with respect to a specific nutrient. Diminished or low status indicates inadequate supply or stores of a specific nutrient for optimal physiological functioning.

Steatosis
the accumulation of fat in the liver.

Stenosis
obstruction or narrowing of a passage. Coronary stenosis refers specifically to obstruction or narrowing of a coronary artery, which supplies blood to the heart muscle (myocardium).

Steroid
a molecule related to cholesterol. Many important hormones, such as estrogen and testosterone, are steroids.

Steroid hormone receptor
a protein within a cell which binds to a specific steroid hormone. Binding of the steroid hormone changes the shape of the receptor protein and activates it, allowing it to activate gene transcription. In this way, a steroid hormone can activate the synthesis of specific proteins.

Stratum corneum
the outer layer of skin; consists of corneocytes that are connected by various proteins and lipids to form a tight barrier around underlying tissue.

Stress fracture
a hairline or microscopic break in a bone, usually due to repetitive stress rather than trauma. Stress fractures are usually painful, and may be undetectable by X-ray. Although they may occur in almost any bone, common sites of stress fractures are the tibia (lower leg) and metatarsals (foot).

Stroke
damage that occurs to a part of the brain when its blood supply is suddenly interrupted (ischemic stroke) or when a blood vessel ruptures and bleeds into the brain (hemorrhagic stroke). A stroke is also called a cerebrovascular accident (CVA).

Subclinical
without clinical signs or symptoms; sometimes used to describe the early stage of a disease or condition, before symptoms are detectable by clinical examination or laboratory tests.

Subcutaneous
under the skin.

Substrate
a reactant in an enzyme-catalyzed reaction.

Sucrose
a disaccharide composed of two monosaccharides: glucose and fructose. Also known as cane sugar or table sugar.

Supplement
a nutrient or phytochemical supplied in addition to that which is obtained in the diet.

Synapse
cell-cell junction that allows chemical or electrical signals to be passed from a neuron to another neuron or muscle cell.

Synaptic plasticity
the ability of neurons to change the number or strength of their synaptic connections. Synaptic plasticity is believed to underlie the processes of learning and memory.

Syndrome
a combination of symptoms that occur together and is indicative of a specific condition or disease.

Synergistic
when the effect of two treatments together is greater than the sum of the effects of the two individual treatments, the effect is said to be synergistic.

Synthesis
the formation of a chemical compound from its elements or precursor compounds.

Systematic review
a structured review of the literature designed to answer a clearly formulated question. Systematic reviews use systematic and explicitly predetermined methods to identify, select and critically evaluate research relevant to the question, and to collect and analyze data from the studies that are included in the review. Statistical methods, such as meta-analysis, may be used to summarize the results of the included studies.

Systemic lupus erythematosus (SLE)
a chronic autoimmune disease characterized by inflammation of the connective tissue. SLE is more common in women than men and may result in inflammation and damage to the skin, joints, blood vessels, lungs, heart, and kidneys.

Systolic blood pressure
the highest arterial pressure measured during the heart beat cycle, and the first number in a blood pressure reading (e.g., 120/80).

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Tannins
any of a large group of plant-derived compounds. Tannins tend to be bitter tasting and may function in pigment formation and plant protection.

Telangiectasias
broken capillaries in the skin.

Telomere
the segment of DNA at each end of a chromosome.

Teratogen
an agent that interferes with normal development of an embryo or fetus.

Tertile
one-third of a sample or population.

Tetany
a condition of prolonged and painful spasms of the voluntary muscles, especially the fingers and toes (carpopedal spasm), as well as the facial musculature.

Thalassemia major
Beta thalassemia is a genetic disorder that results in abnormalities of the globin (protein) portion of hemoglobin. An individual who is homozygous for the β thalassemia gene (has two copies of the β thalassemia gene) is said to have thalassemia major. Infants born with thalassemia major develop severe anemia a few months after birth, accompanied by pallor, fatigue, poor growth, and frequent infections. Blood transfusions are used to treat thalassemia major but cannot cure it.

Thalassemia minor
Individuals who are heterozygous for the β thalassemia gene (carry one copy of the β thalassemia gene) are said to have thalassemia minor or thalassemia trait. These individuals are

generally healthy but can pass the β thalassemia gene to their children and are said to be carriers of the β thalassemia gene.

Thermoregulation
the process of controlling body temperature to prevent both excessive cooling and warming.

Threshold
the point at which a physiological effect begins to be produced, for example, the degree of stimulation of a nerve which produces a response or the level of a chemical in the diet that results in a disease.

Thyroid
a butterfly-shaped gland in the neck that secretes thyroid hormones. Thyroid hormones regulate a number of physiologic processes, including growth, development, metabolism, and reproductive function.

Thyroid follicular cancer
a cancer of the thyroid gland that constitutes about 30% of all thyroid cancers. It has a greater rate of recurrence and metastases (spreading to other organs) than thyroid papillary cancer.

Thyroid papillary cancer
the most common form of thyroid cancer, which most often affects women of childbearing age. Thyroid papillary cancer has a lower rate of recurrence and metastases (spreading to other organs) than thyroid follicular cancer.

Topical
applied to the skin or other body surface.

Total Parenteral Nutrition (TPN)
intravenous (I.V.) feeding that provides patients with essential nutrients when they are too ill to eat normally.

Trabecular bone
also known as spongy or cancellous bone, the type of bone found within the ends of long bones and inside flat bones and spinal vertebrae.

Transcription
(DNA transcription); the process by which one strand of DNA is copied into a complementary sequence of RNA.

Transcription factor
a protein that functions to initiate, enhance, or inhibit the transcription of a gene. Transcription factors can regulate the formation of a specific protein encoded by a gene.

***Trans* fat**
hydrogenated or partially hydrogenated oils.

Transient ischemic attack (TIA)
sometimes called a small or mini stroke. TIAs are caused by a temporary disturbance of blood supply to an area of the brain, resulting in a sudden, brief (usually less than one hour) disruptions in certain brain functions.

Translation
(RNA translation); the process by which the sequence of nucleotides in a messenger RNA (mRNA) molecule directs the incorporation of amino acids into a protein.

Trauma
an injury or wound.

Tremor
trembling or shaking of a part or all of the body.

Triglyceride
lipid consisting of three fatty acid molecules bound to a glycerol backbone. Triglycerides are the principal form of fat in the diet, although they are also synthesized endogenously. Triglycerides are stored in adipose tissue and represent the principal storage form of fat. Elevated serum triglycerides are a risk factor for cardiovascular disease.

Trimethylaminuria
a hereditary disorder characterized by increased urinary excretion of trimethylamine, a compound with a "fishy" or foul odor.

T-score
a clinical measure of bone mineral density (BMD) obtained by dual X-ray absorptiometry (DEXA).

Tuberculosis
an infection caused by bacteria called *mycobacterium tuberculosis*. Many people infected with tuberculosis have no symptoms because it is dormant. Once active, tuberculosis may cause damage to the lungs and other organs. Active tuberculosis is also contagious and is spread through inhalation. Treatment of tuberculosis involves taking antibiotics and vitamins for at least six months.

Typhoid
an infectious disease spread by the contamination of food or water supplies with the bacteria called salmonella typhi. Food and water can be contaminated directly by sewage or indirectly by flies or poor hygiene. Though rare in the US, it is common in some parts of the world. Symptoms include fever, abdominal pain, diarrhea, and a rash. It is treated with antibiotics and intravenous fluids. Vaccination is recommended to those traveling to areas where typhoid is common.

Glossary: U

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UL
tolerable upper intake level. Established by the Food and Nutrition Board of the US Institute of Medicine, the UL is the highest level of daily intake of a specific nutrient likely to pose no risk of adverse health effects in almost all individuals of a specified age.

Ulcerative colitis
a chronic inflammatory disease of the colon and rectum. Symptoms of ulcerative colitis include abdominal pain, cramping, and bloody diarrhea.

Ultrasonography
a test in which high-frequency sound waves (ultrasound) are bounced off tissues and the echoes are converted into a picture (sonogram).

Unsaturated fatty acid
a fatty acid with at least one double bond between carbons.

Uremia
an excessive concentration of urea and other nitrogenous waste products in the blood that are normally excreted by the kidneys.

Uric acid
an antioxidant produced by the body.

Glossary: V

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Vascular dementia
dementia resulting from cerebrovascular disease, for example, a cerebrovascular accident (stroke).

Vascular endothelium
the single cell layer that lines the inner surface of blood vessels. Healthy endothelial function promotes vasodilation and inhibits platelet aggregation (clot formation).

Vascularization
the creation of new blood vessels or the extension of existing blood vessels into tissue.

Vasoconstriction
narrowing of a blood vessel.

Vasodilation
relaxation or opening of a blood vessel.

Vehicle
the material in which a treatment compound is dissolved.

Ventricles
the two lower chambers of the heart that pump blood to the body (left) and the lungs (right).

Vertebral
of or pertaining to a vertebra, 1 of the 23 bones that comprise the spine.

Vesicle
literally a small bag or pouch. Inside a cell, a vesicle is a small organelle surrounded by its own membrane.

Virulent
marked by a rapid, severe, or damaging course.

Virus
a microorganism, which cannot grow or reproduce apart from a living cell. Viruses invade living cells and use the synthetic processes of infected cells to survive and replicate.

Vitamin
an organic (carbon-containing) compound necessary for normal physiological function that cannot be synthesized in adequate amounts and must therefore be obtained in the diet.

VLDL
Very-low-density lipoprotein cholesterol. VLDLs transport lipids in the bloodstream.

Glossary: W, X, Y, Z

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Xenobiotic
a chemical compound that is foreign to the organism. Xenobiotics may include dietary factors, toxins, pharmaceuticals, and pollutants.

Xenobiotic metabolism
a series of enzymatic reactions that convert a foreign chemical compound into an inert substance that can be safely excreted from the body. The three phases of xenobiotic metabolism include: (i) activation, (ii) functionalization, and (iii) efflux.

Xenograft
a transplant of tissue from a donor of one species to a recipient of another species.

Zollinger-Ellison syndrome
a rare disorder caused by a tumor called a gastrinoma, most often occurring in the pancreas. The tumor secretes the hormone gastrin, which causes increased production of gastric acid leading to severe recurrent ulcers of the esophagus, stomach, and the upper portions of the small intestine.

Nutrient Index

Articles on the following nutrients, phytochemicals, food, and beverages are available in the Linus Pauling Institute's Micronutrient Information Center:

Disease Index

- **Alzheimer's Disease**
  - L-Carnitine | Choline | Copper | Curcumin | Essential Fatty Acids | Folate | Fruit and Vegetables | Iron | Moderate Alcohol Consumption | Thiamin | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin D | Vitamin E | Zinc
- **Angina Pectoris**
  - L-Carnitine | Coenzyme Q$_{10}$
- **Asthma**
  - Magnesium | Omega-3 Fatty Acids | Vitamin C
- **Atherosclerosis**
  - Carotenoids | Coenzyme Q$_{10}$ | Copper | Essential Fatty Acids | Flavonoids | Garlic | Iron | Magnesium | Moderate Alcohol Consumption | Resveratrol | Soy Isoflavones | Vitamin C | Vitamin E
- **Athletic Performance**
  - L-Carnitine | Coenzyme Q$_{10}$
- **Autoimmune Disease**
  - Omega-3 Fatty Acids | Vitamin D
- **Bone Health (see the articles: Bone Health In Brief, Bone Health In Depth, and Osteoporosis)**
- **Cancer**
  - **General**
    - L-Carnitine | Carotenoids | Coenzyme Q$_{10}$ | Coffee | Cruciferous Vegetables | Curcumin | Glycemic Index and Glycemic Load | Flavonoids | Fruit and Vegetables | Heavy Alcohol Consumption | Indole-3-Carbinol | Iron | Isothiocyanates | Niacin | Phytosterols | Resveratrol | Riboflavin | Vitamin B$_6$ | Selenium | Tea | Thiamin | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin D | Vitamin E | Whole Grains
  - **Breast Cancer**
    - Alcohol Consumption | Carotenoids | Coenzyme Q$_{10}$ | Coffee | Cruciferous Vegetables | Curcumin | Fiber | Flavonoids | Folate | Fruit and Vegetables | Glycemic Index and Glycemic Load | Iron | Legumes | Lignans | Molybdenum | Riboflavin | Soy Isoflavones | Tea | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin D
  - **Colorectal Cancer**
    - Calcium | Carotenoids | Coffee | Cruciferous Vegetables | Curcumin | Fiber | Folate | Fruit and Vegetables | Garlic | Heavy Alcohol Consumption | Iron | Legumes | Vitamin C | Vitamin D | Whole Grains
  - **Esophageal Cancer**
    - Coffee | Fruit and Vegetables | Heavy Alcohol Consumption | Iron | Molybdenum | Tea | Whole Grains
  - **Gynecologic Cancers**
    - Legumes | Lignans | Soy Isoflavones | Tea
  - **Liver Cancer**
    - Chlorophyllin | Choline | Coffee | Fruit and Vegetables | Heavy Alcohol Consumption | Iron
  - **Lung Cancer**
    - Carotenoids | Coffee | Cruciferous Vegetables | Fruit and Vegetables | Vitamin A | Vitamin D
  - **Prostate Cancer**
    - Calcium | Carotenoids | Coffee | Cruciferous Vegetables | Curcumin | Flavonoids | Legumes | Lignans | Soy Isoflavones | Vitamin D
  - **Gastric Cancer**
    - Coffee | Cruciferous Vegetables | Fruit and Vegetables | Garlic | Sodium | Tea | Vitamin C
- **Cardiac Arrhythmias**
  - Coffee | Heavy Alcohol Consumption | Omega-3 Fatty Acids | Potassium

Cardiovascular Disease

- **General**
  - Calcium | L-Carnitine | Carotenoids | Choline | Chromium | Coenzyme Q$_{10}$ | Copper | Cruciferous Vegetables | Fiber | Flavonoids | Folate | Fruit and Vegetables | Garlic | Glycemic Index and Glycemic Load | Heavy Alcohol Consumption | Iron | Legumes | Lignans | Magnesium | Moderate Alcohol Consumption | Niacin | Nuts | Omega-3 Fatty Acids | Omega-6 Fatty Acids | Phytosterols | Resveratrol | Selenium | Soy Isoflavones | Tea | Thiamin | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin E | Vitamin K | Whole Grains
- **Angina Pectoris**
  - L-Carnitine | Coenzyme Q$_{10}$
- **Atherosclerosis**
  - Carotenoids | Coenzyme Q$_{10}$ | Copper | Essential Fatty Acids | Flavonoids | Garlic | Iron | Magnesium | Moderate Alcohol Consumption | Resveratrol | Soy Isoflavones | Vitamin C | Vitamin E
- **Cardiac Arrhythmias**
  - Coffee | Heavy Alcohol Consumption | Omega-3 Fatty Acids | Potassium
- **Congestive Heart Failure**
  - L-Carnitine | Coenzyme Q$_{10}$ | Moderate Alcohol Consumption | Sodium | Thiamin | Vitamin C | Vitamin D
- **Coronary Heart Disease**
  - Carotenoids | Coffee | Fiber | Fruit and Vegetables | Glycemic Index and Glycemic Load | Iron | Legumes | Magnesium | Moderate Alcohol Consumption | Nuts | Omega-3 Fatty Acids | Omega-6 Fatty Acids | Phytosterols | Resveratrol | Tea | Vitamin C | Whole Grains
- **High Blood Pressure**
  - Calcium | Coenzyme Q$_{10}$ | Coffee | Fiber | Flavonoids | Garlic | Glycemic Index and Glycemic Load | Heavy Alcohol Consumption | Magnesium | Potassium | Riboflavin | Sodium | Tea | Vitamin C | Vitamin D | Whole Grains
- **High Homocysteine**
  - Choline | Coffee | Folate | Legumes | Riboflavin | Vitamin B$_6$ | Vitamin B$_{12}$
- **High Total and LDL Cholesterol**
  - Coffee | Essential Fatty Acids | Fiber | Flavonoids | Garlic | Glycemic Index and Glycemic Load | Niacin | Nuts | Pantothenic Acid | Phytosterols | Soy Isoflavones | Tea | Vitamin C | Whole Grains
- **High Triglycerides**
  - Glycemic Index and Glycemic Load | Niacin | Omega-3 Fatty Acids | Tea | Vitamin C
- **Intermittent Claudication in Peripheral Arterial Disease**
  - L-Carnitine | Moderate Alcohol Consumption
- **Low HDL Cholesterol**
  - Flavonoids | Moderate Alcohol Consumption | Niacin | Regular Physical Activity | Tea
- **Myocardial Infarction**
  - L-Carnitine | Coenzyme Q$_{10}$ | Copper | Fiber | Fruit and Vegetables | Iron | Magnesium | Moderate Alcohol Consumption | Niacin | Nuts | Omega-3 Fatty Acids | Selenium | Tea | Vitamin C | Vitamin E
- **Stroke**
  - Carotenoids | Choline | Coffee | Folate | Glycemic Index and Glycemic Load | Heavy Alcohol Consumption | Magnesium | Moderate Alcohol Consumption | Nuts | Potassium | Tea | Vitamin C | Vitamin E | Whole Grains
- **Carpal Tunnel Syndrome**
  - Vitamin B$_6$
- **Cataracts**
  - Carotenoids | Fruit and Vegetables | Riboflavin | Thiamin | Vitamin C | Vitamin E
- **Celiac Disease**
  - Copper | Iron | Magnesium | Vitamin B$_{12}$ | Zinc
- **Chronic Obstructive Pulmonary Disease (COPD)**
  - Fruit and Vegetables | Isothiocyanates
- **Cirrhosis**
  - Choline | Coffee | Heavy Alcohol Consumption | Iron
- **Cognitive Function (see the articles: Cognitive Function In Brief and Cognitive Function In Depth)**
- **Common Cold (see MIC article)**
  - Vitamin C | Zinc
- **Congestive Heart Failure**
  - L-Carnitine | Coenzyme Q$_{10}$ | Moderate Alcohol Consumption | Sodium | Thiamin | Vitamin C | Vitamin D
- **Coronary Heart Disease**
  - Carotenoids | Coffee | Fiber | Fruit and Vegetables | Glycemic Index and Glycemic Load | Iron | Legumes | Magnesium | Moderate Alcohol Consumption | Nuts | Omega-3 Fatty Acids | Omega-6 Fatty Acids | Phytosterols | Resveratrol | Tea | Vitamin C | Whole Grains
- **Depression**
  - L-Carnitine | Curcumin | Omega-3 Fatty Acids | Vitamin B$_6$ | Vitamin B$_{12}$ | Zinc
- **Diabetes Mellitus**
  - **Gestational Diabetes**
    - Chromium | Omega-3 Fatty Acids | Vitamin D
  - **Type 1 Diabetes**
    - Coenzyme Q$_{10}$ | Niacin | Vitamin D
  - **Type 2 Diabetes**
    - Biotin | L-Carnitine | Chromium | Coenzyme Q$_{10}$ | Coffee | Curcumin | Glycemic Index and Glycemic Load | Fiber | Flavonoids | Fruit and Vegetables | Iron | Legumes | Lipoic Acid | Magnesium | Manganese | Moderate Alcohol Consumption | Nuts | Omega-3 Fatty Acids | Resveratrol | Tea | Vitamin C | Vitamin D | Vitamin E | Whole Grains | Zinc
- **Epilepsy**
  - Manganese
- **Fatty Liver Disease**
  - Choline | Essential Fatty Acids | Vitamin E
- **Friedreich's Ataxia**
  - Coenzyme Q$_{10}$ | Niacin
- **Glaucoma**
  - Choline
- **Growth and Development**
  - Iron | Omega-3 Fatty Acids | Zinc
- **High Blood Pressure**
  - Calcium | Coenzyme Q$_{10}$ | Coffee | Fiber | Flavonoids | Garlic | Glycemic Index and Glycemic Load | Heavy Alcohol Consumption | Magnesium | Potassium | Riboflavin | Sodium | Tea | Vitamin C | Vitamin D | Whole Grains
- **High Homocysteine**
  - Choline | Coffee | Folate | Legumes | Riboflavin | Vitamin B$_6$ | Vitamin B$_{12}$
- **High Total and LDL Cholesterol**
  - Coffee | Essential Fatty Acids | Fiber | Flavonoids | Garlic | Glycemic Index and Glycemic Load | Niacin | Nuts | Pantothenic Acid | Phytosterols | Soy Isoflavones | Tea | Whole Grains
- **High Triglycerides**
  - Glycemic Index and Glycemic Load | Niacin | Omega-3 Fatty Acids | Tea
- **HIV/AIDS**
  - L-Carnitine | Niacin | Selenium | Vitamin A | Zinc
- **Huntington's Disease**
  - Coenzyme Q$_{10}$ | Thiamin
- **Immune Function (see the articles: Immunity In Brief and Immunity In Depth)**
  - Copper | Iron | Pantothenic Acid | Selenium | Vitamin A | Vitamin B$_6$ | Vitamin C | Vitamin D | Vitamin E | Zinc
- **Inflammation (see MIC article)**
- **Inflammatory Bowel Disease**
  - Omega-3 Fatty Acids | Vitamin D
- **Intermittent Claudication in Peripheral Arterial Disease**
  - L-Carnitine | Moderate Alcohol Consumption
- **Kidney Failure/Dialysis**
  - L-Carnitine | Omega-3 Fatty Acids (IgA Nephropathy) | Phosphorus
- **Kidney Stones**
  - Calcium | Potassium | Sodium | Tea | Vitamin B$_6$ | Vitamin C
- **Lead Poisoning**
  - Calcium | Iron | Vitamin C
- **Low HDL Cholesterol**
  - Flavonoids | Moderate Alcohol Consumption | Niacin | Regular Physical Activity | Tea
- **Macular Degeneration**
  - Carotenoids | Fruit and Vegetables | Vitamin E | Zinc
- **Metabolic Syndrome (see MIC)**
  - Chromium | Essential Fatty Acids | Fiber | Iron | Magnesium
- **Migraine Headache**
  - Magnesium | Riboflavin
- **Multiple Sclerosis (MS)**
  - Biotin | Lipoic Acid | Riboflavin | Vitamin D
- **Myocardial Infarction**
  - L-Carnitine | Coenzyme Q$_{10}$ | Copper | Fiber | Fruit and Vegetables | Iron | Magnesium | Moderate Alcohol Consumption | Niacin | Nuts | Omega-3 Fatty Acids | Selenium | Tea | Vitamin C | Vitamin E
- **Neurodegenerative Diseases**
  - **General**
    - Coenzyme Q$_{10}$ | Coffee | Essential Fatty Acids | Flavonoids | Folate | Iron | Soy Isoflavones | Thiamin | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin D | Vitamin E
  - **Alzheimer's Disease**
    - L-Carnitine | Choline | Copper | Curcumin | Essential Fatty Acids | Folate | Fruit and Vegetables | Iron | Moderate Alcohol Consumption | Thiamin | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin D | Vitamin E | Zinc
  - **Friedreich's Ataxia**
    - Coenzyme Q$_{10}$ | Niacin
  - **Glaucoma**
    - Choline
  - **Huntington's Disease**
    - Coenzyme Q$_{10}$
  - **Parkinson's Disease**
    - Coenzyme Q$_{10}$ | Coffee | Copper | Iron | Tea | Vitamin D
- **Osteoporosis (see MIC article)**
  - Calcium | Carotenoids | Copper | Fluoride | Fruit and Vegetables | Lignans | Magnesium | Manganese | Moderate Alcohol Consumption | Potassium | Sodium | Soy Isoflavones | Tea | Vitamin B$_{12}$ | Vitamin D | Vitamin K
- **Parkinson's Disease**
  - Coenzyme Q$_{10}$ | Coffee | Copper | Iron | Tea | Vitamin D
- **Preeclampsia**
  - Calcium | Magnesium | Riboflavin
- **Pregnancy Complications**
  - Alcohol Consumption | Biotin | Calcium | Choline | Chromium | Coffee | Folate | Iodine | Iron | Magnesium | Omega-3 Fatty Acids | Riboflavin | Vitamin A | Vitamin B$_6$ | Vitamin B$_{12}$ | Vitamin C | Vitamin D | Zinc
- **Rheumatoid Arthritis**
  - Curcumin | Omega-3 Fatty Acids | Vitamin D
- **Schizophrenia**
  - Niacin | Omega-3 Fatty Acids
- **Sepsis**
  - Magnesium | Thiamin | Vitamin C | Zinc
- **Skin Health (see MIC article)**
  - Vitamin A | Vitamin C | Vitamin D | Vitamin E | Minerals | Essential Fatty Acids | Peptides
- **Stroke**
  - Carotenoids | Choline | Coffee | Folate | Glycemic Index and Glycemic Load | Heavy Alcohol Consumption | Magnesium | Moderate Alcohol Consumption | Potassium | Tea | Vitamin C | Vitamin E | Whole Grains
- **Tooth Decay**
  - Fluoride | Tea

Relevant Links

US Government Sites

- Cancer.gov Cancer Information
  Current information about cancer from the National Cancer Institute.
- Dietary Guidelines for Americans
  Dietary guidelines published jointly every five years by the Department of Health and Human Services (HHS) and the Department of Agriculture (USDA).
- Dietary Supplements
  US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition
  Information and warnings about dietary supplements from the FDA.
- National Academy of Medicine
  Includes tables of Dietary Reference Intakes for vitamins, minerals, and macronutrients.
- Food and Nutrition Information Center
  Food and nutrition information and resources from the US Department of Agriculture.
- Healthfinder
  A guide to health information from the US Department of Health and Human Services.
- MEDLINE plus
  Health information from the National Library of Medicine.
- National Center for Complementary and Integrative Health
  Information for consumers and practitioners on complementary and alternative therapies.
- National Heart, Lung and Blood Institute Health Information
  Information regarding cardiovascular, lung, and blood diseases, and sleep disorders.
- National Institute on Aging Health Information
  Information and resources regarding aging, Alzheimer's disease, and related disorders.
- National Institute of Diabetes & Digestive & Kidney Disease Health Information
  Health information on diabetes, digestive diseases, endocrine (hormonal) and metabolic diseases, hematologic (blood) diseases, kidney diseases, and nutrition.
- National Library of Medicine PubMed
  A search engine for the MEDLINE database.
- Office of Dietary Supplements at the National Institutes of Health (NIH)
  Information and resources regarding dietary supplements, including dietary supplement fact sheets, a dietary supplement ingredient database, and a dietary supplement label database.
- Osteoporosis and Related Bone Diseases National Resource Center
  NIH resource center for osteoporosis and other bone disease such as Paget's disease, osteogenesis imperfects, and hyperparathyroidism.
- USDA FoodData Central
  Includes a search engine for the nutritional composition of over 8,000 foods.

Dietary Reference Intakes (DRI) and Recommended Dietary Allowances (RDA)

Full text versions of the recent reports by the Food and Nutrition Board of the Institute of Medicine on recommended intakes of specific nutrients

- Dietary Reference Intakes for Phosphorus, Magnesium, and Fluoride
  (1997)
- Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B$_6$, Folate, Vitamin B$_{12}$, Pantothenic Acid, Biotin, and Choline
  (1998)
- Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids
  (2000)
- Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc
  (2001)
- Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients)
  (2002)
- Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate
  (2004)
- Dietary Reference Intakes for Calcium and Vitamin D
  (2010)

Other Health-related Links

- American Cancer Society
  Information and resources on preventing, treating, and coping with cancers.
- American Diabetes Association
  Information and resources for consumers and health professionals on many aspects of diabetes.
- American Heart Association
  Information and resources for consumers and health professionals on prevention and treatment of cardiovascular disease, including heart attack and stroke.
- National Osteoporosis Foundation
  Information and resources for consumers and health professionals on osteoporosis.
- American Federation for Aging Research
  Current research on healthy aging.

Books

Giving

Español

Your Support Allows Us to Keep the Micronutrient Information Center Freely Available

Your gift will help us maintain and improve the Micronutrient Information Center; 95% of your donation will go directly to fund article updates by our Ph.D. nutrition scientists. Contributions are made through the Oregon State University Foundation, the Institute's parent charity. All gifts are treated as restricted gifts to the Linus Pauling Institute's Micronutrient Information Center and are tax deductible under IRS regulations. *More information about the Institute's fundraising policies and relationships with Oregon State University*

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Contact:

Andrew Norwood
Director of Development
OSU Foundation & Alumni Association
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Phone: 503-273-4420
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Español

Drug-Nutrient Interactions

Although drug-nutrient interactions have not been systematically studied, there are a number of known interactions reported in the scientific literature. The interactions listed in **Table 1** are not meant to be comprehensive but include some of the more common clinically relevant drug-nutrient interactions, especially in the context of micronutrient inadequacy. For additional references on drug-nutrient interactions, see Table 2.

It is important to note that specific criteria to label interactions as "clinically significant" have not been established, although a threshold of ≥20% change in the kinetic and/or dynamic parameter of the drug or nutrient has been proposed (1). Long-term use of the drug is often needed to reach such a threshold and for clinical symptoms of the drug-nutrient interaction to manifest (1).

Table 1. Select Interactions between Drugs and Nutrients

Drug	Micronutrient	Mechanism(s) of Action	Potential Action(s) to Minimize Risk	Reference
Alcohol	Folate	Chronic alcohol abuse has been associated with folate deficiency due to low dietary intake, decreased intestinal absorption, impaired hepatic uptake, and increased excretion of the vitamin.	Ensure adequate intake of folate through diet and/or a daily multivitamin.	(2)
	Riboflavin	Chronic alcohol abuse has been associated with riboflavin deficiency, presumably due to low dietary intake.	Ensure adequate intake of riboflavin through diet and/or a daily multivitamin.	(3)
	Thiamin	Chronic alcohol abuse is associated with thiamin deficiency due to low dietary thiamin intake, impaired absorption and utilization of thiamin, and increased excretion of thiamin.	Thiamin supplementation in alcoholics may prevent Wernicke-Korsakoff's syndrome.	(4)
	Vitamin A	Chronic alcohol abuse depletes the liver of retinol and increases retinol mobilization to extra-hepatic tissues, although the mechanisms are not understood.	Avoid high doses of vitamin A and β-carotene in alcoholics because chronic alcohol abuse increases the risk of retinol-induced hepatotoxicity.	(5, 6)
	Vitamin B$_6$	Low vitamin B$_6$ status in alcoholics may result from inadequate intake and potentially from altered metabolism, although the mechanisms are not fully understood.		(7, 8)
Alendronate (Binosto; Fosamax): see Bisphosphonates				
Amiloride: see Potassium-sparing diuretics				
Antacids	Folate	Use of antacids may slightly impair absorption of synthetic folic acid from supplements due to gastrointestinal pH changes.	Separate folic acid supplementation and drug use by 3 hours.	(9)
	Fluoride	Use of aluminum-containing antacids can decrease fluoride absorption.	Separate antacid intake and fluoride supplements by at least 2 hours.	(10)
	Iron	Use of antacids increases the pH of gastrointestinal contents, which may lead to reduced iron solubility and decreased intestinal absorption of iron.	Separate antacid intake and iron supplements by at least 2 hours.	(11-13)
	Magnesium	Use of magnesium-containing antacids can result in hypermagnesemia in those with impaired renal function since the mineral is not properly excreted.	This might only occur with long-term antacid use; prudent to monitor magnesium intake and magnesium status in patients with renal insufficiency.	(14)
	Manganese	Use of magnesium-containing antacids may decrease absorption of manganese from food or supplements.	Separate antacids and manganese intake by at least 2 hours.	(15)
	Phosphate	Use of aluminum-containing antacids may decrease phosphate absorption and cause hypophosphatemia at high doses.	Hypophosphatemia is usually only a concern with excessive antacid use and very low dietary intake of phosphorus.	(16)
Antibiotics: see Chloramphenicol; Cycloserine; Ethambutol (Myambutol); Isoniazid; Rifampin/Rifampicin (Rifadin); Tetracycline-class antibiotics; Trimethoprim (Primsol); and Quinolone-class antibiotics				
Aspirin	Vitamin C	High doses of aspirin may increase urinary excretion of vitamin C; aspirin might also impair vitamin C absorption in the small intestine. Vitamin C may protect against aspirin-induced damage of the gastric mucosa, possibly through inhibition of iNOS expression.	Long-term use of aspirin might impair vitamin C status. Ensure adequate vitamin C intake from diet and/or supplements.	(17, 18)
	Vitamin E	High doses of supplemental vitamin E may potentiate the antiplatelet effects of aspirin.	Avoid high-dose vitamin E supplements in those taking aspirin.	(19)
Bisphosphonates (alendronate [Binosto, Fosamax], etidronate, ibandronate [Boniva], pamidronate, risedronate [Actonel, Atelvia], zoledronic acid [Reclast])	Calcium	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.	(20)
	Iron	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.	(15, 20)
	Magnesium	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.	(15, 20)
	Zinc	Concomitant intake may decrease bisphosphonate and zinc absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.	(15)
Bumetanide (Bumex): see Loop diuretics				
Calcitriol (Rocaltrol) and some vitamin D analogs	Phosphate	High doses of calcitriol and some vitamin D analogs may increase intestinal calcium/phosphate absorption and cause hypercalcemia/hyperphosphatemia.	Be aware of a possible interaction in patients with chronic kidney disease.	(21)
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	Biotin	Carbamazepine may competitively inhibit intestinal absorption of biotin, inhibit renal reabsorption of biotin, as well as accelerate biotin catabolism.	Biotin status might be impaired with long-term carbamazepine therapy, although the clinical significance of marginal biotin deficiency is unclear.	(22, 23)
	Grapefruit (flavonoids)	The flavonoids in grapefruit inhibit CYP3A4, increasing the bioavailability and risk of toxicity from carbamazepine.		(24)
	Psyllium	When taken at the same time, psyllium may reduce the intestinal absorption of carbamazepine.	Separate taking carbamazepine and psyllium supplements by at least 2 hours.	(15, 25)
Chloramphenicol	Folate	Chloramphenicol has been documented to induce aplastic anemia in rare cases. Chloramphenicol use might reduce the efficacy of supplemental folic acid by interfering with the hematopoietic response.	Monitor hematological parameters in patients taking chloramphenicol.	(12, 26, 27)
	Vitamin B$_{12}$	Chloramphenicol has been documented	Monitor vitamin B$_{12}$ status in patients taking	(12, 26, 28, 29)

		to induce aplastic anemia in rare cases. Chloramphenicol can cause bone marrow suppression. The drug may decrease intestinal absorption of food-bound, but not supplemental, vitamin B_{12} and possibly interfere with the efficacy of supplemental vitamin B_{12} to treat anemia.	chloramphenicol. Multivitamin or single-nutrient vitamin B_{12} supplementation would be needed with long-term drug treatment.	
	Iron	Chloramphenicol has been documented to induce aplastic anemia in rare cases. Chloramphenicol can cause bone marrow suppression; the efficacy of supplemental iron to treat anemia may be affected by chloramphenicol use.	Monitor iron status in patients taking chloramphenicol. Use the lowest effective dose (<25-30 mg/kg) or select a different antibiotic.	(26, 28, 29)
Chlorothiazide (Diuril, Sodium Diuril): see Thiazide diuretics				
Chlorpromazine (Thorazine)	Riboflavin	Chlorpromazine has been shown to inhibit the incorporation of riboflavin into FAD and FMN, as well as increase urinary excretion of riboflavin in the context on inadequate dietary intake of riboflavin.	Available data come from rodent models as human data are lacking. Assess riboflavin status, and if needed, consider a riboflavin-containing supplement. Separate drug from riboflavin supplements by at least 4 hours to minimize interaction.	(12, 30, 31)
Chlortetracycline: see Tetracycline-class antibiotics				
Chlorthalidone (Hygroton, Thalitone): see Thiazide diuretics				
Cholestyramine (Prevalite, Questran, Questran Light)	Folate	Cholestyramine can bind to folate polyglutamates and decrease absorption of folate from food, thus increasing the risk of folate deficiency.	Folic acid supplementation may help prevent deficiency in patients on long-term cholestyramine therapy. Advise taking folic acid supplements 1 hour before or 4-6 hours following drug intake.	(12, 32)
	Vitamin A	Through interfering with fat absorption, cholestyramine might decrease the absorption of vitamin A.	Separate drug and vitamin supplementation by at least 4 hours.	(15, 32)
	Vitamin B_{12}	Cholestyramine might decrease intestinal absorption of vitamin B_{12}, perhaps by binding to intrinsic factor, which is needed for ileal vitamin absorption.	The extent of such an interaction is not clear, as a study in children found that long-term administration of cholestyramine did not alter serum cobalamin. Monitor vitamin B_{12} status; measuring methylmalonic acid is the specific indicator of vitamin B_{12} deficiency.	(32, 33)
	Vitamin D	Through interfering with bile acids and fat absorption, cholestyramine might decrease the absorption of vitamin D.	Separate drug and vitamin D supplementation by at least 4 hours.	(34)
	Vitamin E	Cholestyramine may theoretically decrease the absorption of fat-soluble vitamins, including vitamin E, through interfering with fat absorption.	Separate drug and vitamin E supplementation by at least 4 hours.	(32)
	Vitamin K	There have been a few case reports of bleeding in those taking cholestyramine. Through interfering with bile acids and fat absorption, cholestyramine might decrease the absorption of vitamin K.	Long-term administration of cholestyramine to children did not affect prothrombin time. To avoid a potential interaction, separate drug and vitamin supplementation by at least 4 hours.	(32, 35, 36)
	Minerals	Cholestyramine might impair intestinal absorption of various minerals (e.g., iron, magnesium, zinc); increased urinary excretion of calcium and magnesium has also been documented.	Human data on the effect of cholestyramine on mineral balance are lacking. Multivitamin/mineral supplementation may help ensure adequacy; separating drug and nutrient supplementation by at least 4 hours would prevent any interaction.	(37, 38)
	Carotenoids	Cholestyramine may inhibit intestinal absorption of carotenoids.	Separate drug and nutrient supplementation by at least 4 hours.	(15)
	Psyllium	Psyllium might enhance the lowering of cholesterol by cholestyramine.		(15)
Cimetidine (Cimetidine Acid Reducer [OTC], Tagamet, Tagamet HB): see Histamine-2 receptor antagonists				
Colchicine (Colcrys, Gloperba, Mitigare)	Vitamin B_{12}	Colchicine may decrease the absorption of vitamin B_{12} from food by disrupting normal function of the ileal mucosa.	Prudent to monitor vitamin B_{12} status in patients taking colchicine; methylmalonic acid buildup is the specific indicator of vitamin B_{12} deficiency.	(39, 40)
Colestipol (Colestid, Colestid Flavored)	Folate	Colestipol may bind to folate polyglutamates and might decease absorption of folate from food, increasing the risk of folate deficiency.	Studies are limited. Folic acid supplementation may help prevent deficiency in patients on long-term colestipol therapy. Advise taking folic acid supplements 1 hour before or 4-6 hours following drug intake.	(41-43)
	Fat-soluble vitamins (vitamins A, D, E, K) and carotenoids	As a bile acid sequestrant, colestipol may interfere with the absorption of fat-soluble vitamins and carotenoids.	Studies are limited and have not shown major effects. Monitor patients on long-term colestipol therapy.	(41, 42, 44)
	Iron	Colestipol and iron may form a chelation complex, decreasing intestinal absorption of iron.	Human data are lacking. Separate drug and iron supplements by at least 4 hours.	(45)
Cycloserine	Vitamin B_6	Cycloserine forms an inactive covalently bound complex with pyridoxal 5'-phosphate and may cause a functional vitamin B_6 deficiency, possibly leading to anemia and peripheral neuropathy.	Vitamin B_6 supplementation (≤50 mg/day) might help prevent deficiency.	(12, 46, 47)
Demeclocycline: see Tetracycline-class antibiotics				
Dexlansoprazole (Dexilant): see Proton-pump inhibitors				
Digoxin (Digitek, Digox, Lanoxin, Lanoxin Pediatric)	Calcium	High doses of supplemental calcium could increase the occurrence of abnormal heart rhythms in those taking digoxin due to calcium elevations in plasma and cardiomyocytes, influencing heart contractility and frequency.	Consider advising patients to maintain a stable intake of calcium and avoid daily fluctuations in intake. Monitor serum concentrations of calcium in patients taking digoxin.	(12, 48)
	Magnesium	Digoxin causes reductions in intracellular magnesium concentrations, as well as increased urinary excretion of the mineral. Magnesium-containing antacids or magnesium supplements may decrease digoxin absorption, which may decrease drug efficacy. Hypomagnesemia may increase the risk for digoxin toxicity through a number of mechanisms, including inhibition of the magnesium-dependent enzyme Na^+/K^+-ATPase and increased activity of the Na^+/Ca^{2+} exchanger, thereby increasing intracellular calcium.	Separate drug and any magnesium supplements by at least 2 hours. Monitor magnesium status in patients taking digoxin.	(49, 50)
Diuretics (see Loop diuretics, Potassium-sparing diuretics, Thiazide diuretics)				
Doxorubicin (Adriamycin)	Riboflavin	Doxorubicin may inhibit the incorporation of riboflavin into active coenzyme, FAD, due to structural similarities.	Available data come from rodent models; human data are lacking. Separate drug and riboflavin intake by at least 4 hours to avoid any interaction; consider riboflavin supplementation.	(12, 51)
Doxycycline (Acticlate, Avidoxy, Doryx, Doryx MPC, Doxy 100, Mondoxyne NL, Morgidox, Oracea, Soloxide, Targadox, Vibramycin): see Tetracycline-class antibiotics				
Eplerenone (Inspra): see Potassium-sparing diuretics				
Eravacycline (Xerava): see Tetracycline-class antibiotics				
Esomeprazole (Esomep-EZS, GoodSense Esomeprazole [OTC], Nexium, Nexium 24HR [OTC], Nexium I.V.): see Proton-pump inhibitors				
Ethacrynic acid (Edecrin, Sodium Edecrin): see Loop diuretics				
Ethambutol (Myambutol)	Zinc	Ethambutol chelates zinc, which could prevent its absorption. This might increase the risk of zinc deficiency and associated visual impairments, including optic neuropathy.	Zinc supplementation may be needed, but long-term, excessive zinc supplementation can cause copper deficiency.	(52-54)
	Copper	Ethambutol chelates copper, but the exact MOA that leads to optic neuropathy is not known.	Separate drug and copper supplements by at least 2 hours. Due to the potential for ocular toxicity, it is prudent to closely monitor visual function, including changes in color vision.	(12, 52, 55)
Etidronate: see Bisphosphonates				
Famotidine (Acid Controller Max St [OTC], Acid Controller Original Str [OTC], Acid Reducer [OTC], Acid Reducer Maximum Strength [OTC], Famotidine Maximum Strength [OTC], Heartburn Relief [OTC], Heartburn Relief Max St [OTC], Heartburn Relief Max St [OTC], Pepcid, Pepcid AC Maximum Strength [OTC]): see Histamine-2 receptor antagonists				
Fluoroquinolone-class antibiotics (see Quinolone-class antibiotics)				
Fluorouracil (5-Fluorouracil)	Niacin	Use of 5-fluorouracil increases the reliance on dietary niacin by interfering with the tryptophan-kynurenine-niacin pathway, which converts tryptophan to nicotinamide adenine dinucleotide (NAD).	Oral niacin supplementation has been shown to relieve deficiency symptoms.	(56-58)
	Thiamin	5-Fluorouracil use may lead to thiamin deficiency as the drug inhibits the phosphorylation of thiamin to thiamin diphosphate/thiamin pyrophosphate, a required enzymatic cofactor in glucose and amino acid metabolism.		(59, 60)
Furosemide (Lasix): see Loop diuretics				
Histamine-2 (H_2) receptor antagonists (cimetidine [Cimetidine Acid Reducer [OTC], Tagamet, Tagamet HB], famotidine [Acid Controller Max St [OTC], Acid Controller Original Str [OTC], Acid Reducer [OTC], Acid Reducer Maximum Strength [OTC], Famotidine Maximum Strength [OTC], Heartburn Relief [OTC], Heartburn Relief Max St [OTC], Pepcid, Pepcid AC Maximum Strength [OTC]], nizatidine)	Vitamin B_{12}	Use of H_2 receptor antagonists may decrease the absorption of food-bound, but not supplemental, vitamin B_{12} due to decreased gastric acidity (gastric acid is needed to liberate the vitamin from proteins in food). Long-term drug use might result in vitamin B_{12} deficiency.	Monitor vitamin B_{12} status (buildup of methylmalonic acid), and consider vitamin B_{12} supplementation with long-term drug use.	(61, 62)
	Calcium	Decreased gastric acidity may impair release of ionized calcium from insoluble calcium salts (calcium carbonate and calcium phosphate), potentially decreasing its absorption in the upper small intestine.	Meet the RDA of calcium from dietary sources. If supplementation is needed, consider the calcium citrate form.	(63)
	Iron	Long-term use might decrease absorption of iron and thus decrease iron status, but this interaction may not be clinically significant.	Separate iron supplementation and drug use by at least 2 hours.	(64)
HMG-CoA reductase inhibitors (statins; atorvastatin [Lipitor], fluvastatin [Lescol XL], lovastatin [Altoprev], pitavastatin [Livalo, Zypitamag], pravastatin [Pravachol], rosuvastatin [Crestor, Ezallor Sprinkle], simvastatin [FloLipid, Zocor])	Nicotinic acid	Some case reports of co-administration of nicotinic acid with an HMG-CoA reductase inhibitor raise concern for an increased risk of myopathy and rhabdomyolysis; the mechanism is not known. Data from clinical trials are largely lacking, and it is not known whether the risk is higher than that associated with HMG-CoA reductase inhibitor monotherapy.	Patients should be aware of possible symptoms of myopathy and rhabdomyolysis and report any symptoms immediately to their healthcare provider.	(65, 66)
	Pantethine (metabolite of pantothenic acid)	Concomitant use of pantethine with any cholesterol-lowering drug may have additive effects on blood cholesterol.		(67, 68)
	Grapefruit	Grapefruit consumption inhibits intestinal CYP3A4 and may increase drug bioavailability and thus increase the risk of drug toxicity, especially HMG-CoA reductase inhibitors with low bioavailability (e.g., atorvastatin, lovastatin, and simvastatin).	Eliminate grapefruit from the diet in patients taking certain HMG-CoA reductase inhibitors, e.g., atorvastatin, lovastatin, or simvastatin. Alternatively, consider a statin that is not metabolized by CYP3A4, such as pravastatin or pitavastatin.	(69)
	Plant stanols or plant sterols	Concomitant use of plant stanols or sterols with any cholesterol-lowering drugs may have additive effects on blood cholesterol.		(70, 71)
Hydrochlorothiazide: see Thiazide diuretics				
Hydroflumethiazide: see Thiazide diuretics				
Ibandronate (Boniva): see Bisphosphonates				
Indapamide: see Thiazide diuretics				
Isoniazid	Niacin	Indirect interaction as the drug affects vitamin B_6-dependent enzymes (see Isoniazid and vitamin B_6). Vitamin B_6 is a cofactor for kynureninase in the tryptophan-kynurenine pathway that converts tryptophan to nicotinamide adenine dinucleotide (NAD); inhibition of kynureninase can lead to niacin deficiency.	Niacin supplementation may be needed during long-term isoniazid treatment.	(72-76)
	Vitamin B_6	Isoniazid may cause a functional vitamin B_6 deficiency, leading to peripheral neuropathy, by forming an inactive, covalently bound complex with pyridoxal 5'-phosphate (PLP). The drug has also been shown to inhibit select PLP-dependent enzymes.	Consider vitamin B_6 supplementation in those taking isoniazid to prevent peripheral neuropathy.	(46, 77, 78)
	Vitamin K	When taken by pregnant women, isoniazid might increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants. Only case reports are available; there are no data on MOA.	Report of possible interaction comes from two case reports where isoniazid, rifampicin, and ethambutol were all administered during pregnancy.	(79)
Ketoconazole	Vitamin D	Ketoconazole inhibits 25-hydroxyvitamin D_3-1α-hydroxylase, including the renal enzyme, and has been found to reduce serum 1α,25-hydroxyvitamin D (calcitriol) concentrations.	Monitor vitamin D status, including 1,25$(OH)_2$D concentrations, in patients taking oral ketoconazole.	(80-82)
Lansoprazole (GoodSense Lansoprazole [OTC], Heartburn Treatment 24 Hour [OTC], Prevacid, Prevacid SoluTab, Prevacid 24HR [OTC]): see Proton-pump inhibitors				
Levodopa with carbidopa (Duopa, Rytary, Sinemet)	Folate	Levodopa use may increase blood concentrations of homocysteine: levodopa methylation by catechol O-methyltransferase and S-adenosylmethionine produces S-adenosylhomocysteine, which is converted to homocysteine.	Adequate dietary folate intake and/or folic acid (and other B vitamin) supplementation may help decrease homocysteine concentrations in patients taking levodopa.	(83, 84)
	Vitamin B_6	Levodopa can form a covalent complex with pyridoxal 5'-phosphate and limit its bioavailability, creating a functional vitamin B_6 deficiency. High-dose pyridoxine supplementation has been found to decrease the efficacy of levodopa due to acceleration of levodopa-to-dopamine metabolism peripherally, thereby reducing availability of levodopa to the CNS.	Avoid vitamin B_6 supplementation with levodopa monotherapy. Co-administer levodopa with a dopamine decarboxylase inhibitor, such as carbidopa.	(15, 85-87)
	Iron	Levodopa/carbidopa may bind to iron and reduce absorption of both iron and the drug.	Separate drug and iron intake by at least 2 hours.	(88, 89)
Levothyroxine (Euthyrox, Levoxyl, Synthroid, Tirosint, Tirosint-SOL, Unithroid)	Calcium	Concomitant intake of levothyroxine and calcium supplements may decrease levothyroxine absorption, likely due to the formation of an insoluble complex. This interaction could decrease drug efficacy.	Separate levothyroxine and calcium supplementation by at least 4 hours. Preliminary evidence indicates that liquid levothyroxine might be less affected by concomitant mineral intake compared to tablet levothyroxine.	(90-93)
	Iron	Concomitant intake of levothyroxine and ferrous sulfate supplements may decrease the efficacy of levothyroxine, likely due to formation of an insoluble complex.	Separate levothyroxine and iron supplements by at least two hours. Preliminary evidence indicates that liquid levothyroxine might be less affected by concomitant mineral intake compared to tablet levothyroxine.	(93-95)
Lithium (Lithobid)	Iodide	Concomitant use of lithium and pharmacological doses of potassium iodide may increase the risk of hypothyroidism due to inhibition of thyroid hormone synthesis (i.e., Wolff-Chaikoff effect).	Monitor thyroid status in patients taking lithium.	(15, 96)
	Psyllium	According to a case report, psyllium supplementation may decrease lithium absorption. Psyllium seeds are rich in polysaccharides and may interfere with drug absorption.	Separate taking psyllium supplements and drug by at least 2 hours to avoid any possible interaction.	(15, 97)
Loop diuretics (bumetanide [Bumex], ethacrynic acid [Edecrin, Sodium Edecrin]; furosemide [Lasix], torsemide)	Magnesium	If taken for an extended period of time, high doses of loop diuretics can interfere with renal reabsorption of magnesium, increase urinary excretion of magnesium, and result in magnesium depletion.	Monitor magnesium status (dietary, serum, and urinary magnesium) in patients on long-term therapy with loop diuretics.	(98-100)
	Potassium	Use of loop diuretics can increase urinary excretion of potassium and may result in hypokalemia.		(101)
	Thiamin	By increasing urinary flow, loop diuretics (especially furosemide) may prevent renal reabsorption of thiamin, thereby increasing urinary excretion of thiamin and increasing risk of thiamin deficiency.	A daily multivitamin containing thiamin may help prevent deficiency.	(102-104)
Lymecycline: see Tetracycline-class antibiotics				
Metformin (Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet, Riomet ER)	Vitamin B_{12}	Metformin interferes with ileal absorption of the intrinsic factor-vitamin B_{12} complex.	Monitor vitamin B_{12} status; measuring methylmalonic acid, in blood or urine, is a specific indicator of deficiency.	(105)
	Guar gum (Cyamopsis tetragonolobus)	When taken concurrently, guar gum may slow the absorption of metformin and decrease the amount absorbed.		(106)
Methyclothiazide: see Thiazide diuretics				
Methyldopa	Iron	Concomitant intake of methyldopa and ferrous sulfate or ferrous gluconate supplements may decrease the efficacy of methyldopa due to decreased intestinal drug absorption. MOA is unknown but postulated to be due to complex formation.	Separate drug and iron supplements by at least 4 hours.	(107, 108)
Methotrexate (Otrexup, Rasuvo, RediTrex, Trexall, Xatmep)	Folate	Methotrexate inhibits enzymes involved in nucleotide synthesis, including dihydrofolate reductase. Due to its antagonism, methotrexate use can lead to folate deficiency.	Supplementation with folic or folinic acid (leucovorin), which is recommended for patients with rheumatoid arthritis, reduces the antifolate toxicity.	(109-111)
Metolazone: see Thiazide diuretics				
Nitrous oxide	Vitamin B_{12}	Nitrous oxide oxidizes and inactivates vitamin B_{12}, thus inhibiting both of the vitamin B_{12}-dependent enzymes, methionine synthetase and L-methylmalonyl-coenzyme A mutase. This can produce many of the clinical features of vitamin B_{12} deficiency, including megaloblastic anemia and neuropathy.	Since nitrous oxide is commonly used for surgery in the elderly, consider ruling out vitamin B_{12} deficiency prior to its use.	(112, 113)
Nizatidine: see Histamine-2 receptor antagonists				
Olestra (Olean)	Fat-soluble vitamins	Olestra may sequester fat-soluble nutrients and cause impaired absorption of carotenoids and fat-soluble vitamins; vitamins A, D, E, and K may be added to olestra-containing foods for this reason.	The clinical significance of this interaction is not clear.	(114-116)
Omadacyclin (Nuzyra): see Tetracycline-class antibiotics				
Omeprazole (Acid Reducer [OTC], Prilosec, Prilosec OTC [OTC]): see Proton-pump inhibitors				
Orlistat (Alli [OTC], Xenical)	Fat-soluble vitamins	Orlistat may decrease the intestinal absorption of carotenoids and fat-soluble vitamins (vitamins A, D, E, and K).	Orlistat and vitamin supplements should be separated by at least 2 hours.	(117-121)
Oxytetracycline: see Tetracycline-class antibiotics				
Pamidronate: see Bisphosphonates				
Pantoprazole (Protonix): see Proton-pump inhibitors				
Penicillamine (Cuprimine, Depen Titratabs)	Vitamin B_6	Penicillamine may cause a functional vitamin B_6 deficiency by forming an inactive, thiazolidine complex with pyridoxal 5'-phosphate. This complex formation may also impair penicillamine action.	Supplemental pyridoxine has been used to prevent vitamin B_6 deficiency and may be considered in those with low vitamin B_6 status. Separating drug and supplement intake by at least 2 hours may help minimize the interaction.	(12, 122, 123)
	Copper	Penicillamine chelates copper and increases its urinary excretion.	It is generally advised that patients taking penicillamine to reduce copper status (e.g., in Wilson's disease) limit copper intake from food and avoid any copper-containing supplements.	(12)
	Iron	Penicillamine chelates iron and increases its excretion. Concomitant intake of penicillamine and iron supplements decreases drug absorption and efficacy. Discontinuation of oral iron supplements while on penicillamine therapy has been associated with glomerulonephritis, presumably due to increased drug absorption and toxicity.	Separate drug and iron supplements by at least 2 hours.	(124, 125)
	Magnesium	Magnesium and penicillamine may complex together and prevent intestinal absorption of both magnesium and the drug.	Separate drug and magnesium supplements or magnesium-containing antacids by at least 2 hours. Assess magnesium status before high-dose penicillamine.	(12, 124)
	Zinc	Penicillamine is a metal chelator, and its use may reduce intestinal absorption of zinc and increase its excretion, increasing risk of zinc deficiency. Use of zinc supplements may decrease the absorption of penicillamine.	Separate drug and zinc supplements by at least 2 hours. Closely monitor patients as zinc supplementation can reduce copper status through inhibiting copper absorption and increasing copper excretion.	(12, 126)
Phenytoin (Dilantin, Dilantin Infatabs, Phenytek)	Folate	Phenytoin inhibits the intestinal absorption of folate and lowers serum folate concentrations. Supplementation with high-dose folic acid may lead to decreased serum concentrations of phenytoin.	Long-term phenytoin use may decrease folate status. Folic acid supplementation is often recommended when beginning phenytoin. Closely monitor serum concentrations of phenytoin.	(127-129)
	Thiamin	Lower blood concentrations of thiamin have been reported in those taking phenytoin for epilepsy. MOA is not known.	Research is limited. Monitor thiamin status and consider thiamin supplementation if necessary.	(130, 131)
	Vitamin B_6	Extremely high dosages of pyridoxine (≥80 mg/day) have been associated with decreased phenytoin concentrations in patients taking multiple anticonvulsants for epilepsy. MOA is not known.	Avoid high doses of pyridoxine.	(132)
	Vitamin D	Phenytoin use has resulted in decreased serum concentrations of 25-hydroxyvitamin D, perhaps due to increased metabolism of vitamin D to inactive metabolites in the liver.	Long-term phenytoin use may require vitamin D and calcium supplementation to prevent deleterious effects on bone health.	(133-135)
	Vitamin K	Phenytoin may increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants when taken by pregnancy women. MOA hypothesized to include induction of fetal hepatic enzymes that increase oxidative degradation of vitamin K.	Hemorrhagic disease of the newborn may be more serious in newborns of women treated with anticonvulsants. Vitamin K is administered to newborns immediately after birth to prevent hemorrhagic disease.	(136)
	Piperine (in some curcumin supplements)	Piperine may increase the bioavailability and slow the elimination of phenytoin through interfering with efflux drug transporters and phase I cytochrome P450 enzymes.	Data on an interaction are limited.	(137, 138)
Polythiazide (Renese): see Thiazide diuretics				
Potassium-sparing diuretics (amiloride, eplerenone [Inspra], spironolactone [Aldactone, CaroSpir], triamterene [Dyrenium])	Folate	Triamterene impairs intestinal absorption of folate and inhibits dihydrofolate reductase, which converts dihydrofolate to the active form of folate, tetrahydrofolate.	Encourage patients on long-term triamterene therapy to consume the RDA for folate through diet and/or supplements. Measuring folate concentrations in red blood cells is a better indicator of folate status than serum folate concentrations.	(109, 139)
	Phosphate	If taken with phosphate supplements, potassium-sparing diuretics may result in hyperkalemia.	Be aware of the potential interaction and of supplement intake by patients.	(16)
	Zinc	Some, but not all, studies have found that amiloride use decreases urinary excretion of zinc – the effect may depend on drug dosage. One small study found no effect of triamterene on urinary excretion of zinc.	Amiloride has been used in combination with thiazide diuretics to mitigate the risk of zinc depletion.	(140-142)
Proton-pump inhibitors (dexlansoprazole [Dexilant], esomeprazole [Esomep-EZS, GoodSense Esomeprazole [OTC], Nexium, Nexium 24HR Clear Minis [OTC], Nexium 24HR [OTC], Nexium I.V.], lansoprazole [GoodSense Lansoprazole [OTC], Heartburn Treatment 24 Hour [OTC], Prevacid, Prevacid 24HR [OTC], Prevacid SoluTab], omeprazole [Acid Reducer [OTC], Prilosec, Prilosec [OTC]], pantoprazole [Protonix], rabeprazole [Aciphex, AcipHex Sprinkle])	Vitamin B_{12}	Use of proton-pump inhibitors may decrease the absorption of food-bound, but not supplemental, vitamin B_{12} due to decreased gastric acidity (gastric acid is needed to liberate the vitamin from proteins in food). Long-term drug use can result in vitamin B_{12} deficiency.	Monitor vitamin B_{12} status (buildup of methylmalonic acid), and consider vitamin B_{12} supplementation with long-term drug use.	(143, 144)
	Calcium	Decreased gastric acidity may impair release of ionized calcium from insoluble calcium salts (calcium carbonate and calcium phosphate), potentially decreasing its absorption in the upper small intestine.	Meet the RDA of calcium from dietary sources. If supplementation is needed, consider the calcium citrate form.	(63)
	Iron	Long-term use of proton-pump inhibitors might decrease intestinal absorption of iron and iron status, but this interaction may not be clinically significant.	Separate iron supplementation and drug use by at least 2 hours.	(64)
	Phosphate	A reduction in stomach acidity may limit efficacy of oral phosphate-binder therapy in patients with kidney failure.		(145)
Pyrimethamine (Daraprim)	Folate	Pyrimethamine has been shown to competitively inhibit dihydrofolate reductase. Supplemental folic acid may interfere with the antitoxoplasmic effect of the drug, sulfadoxine/pyrimethamine.	Consider supplemental folinic acid.	(146, 147)
Quinolone-class antibiotics (ciprofloxacin [Cipro]; gemifloxacin; levofloxacin; lomefloxacin [Maxaquin]; moxifloxacin; ofloxacin)	Calcium	Concomitant administration of calcium supplements and quinolone antibiotics may decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Separate antibiotic dose by 2 hours before or 6 hours after calcium intake from food (including calcium-fortified foods) and supplements, or from calcium-containing drugs (e.g., antacids).	(148-152)
	Iron	Concomitant administration of ferrous sulfate supplements and quinolone antibiotics may decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Separate antibiotic dose by 2 hours before or 6 hours after iron intake from food or supplements.	(12, 153, 154)
	Magnesium	Concomitant administration of magnesium supplements and quinolone antibiotics might decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Studies are lacking, but an interaction may occur given the reported interaction with magnesium-containing antacids and ciprofloxacin, although the antacids studied also contained aluminum hydroxide. Prudent to separate antibiotic dose by 2 hours before or 6 hours after magnesium supplements.	(155-157)
	Zinc	Concomitant administration of zinc supplements and quinolone antibiotics might decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Research is limited. Separating antibiotic dose by 2 hours before or 6 hours after zinc intake from food or supplements would help minimize any interaction.	(154)
Rabeprazole (Aciphex, AcipHex Sprinkle): see Proton-pump inhibitors				
Rifampin/Rifampicin (Rifadin)	Vitamin D	Rifampin may increase the metabolism of vitamin D to inactive metabolites by induction of liver enzymes, thereby decreasing serum concentrations of 25-hydroxyvitamin D.	Vitamin D supplementation may be needed.	(158)
	Vitamin K	When taken by pregnant women, rifampin might increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants. Only case reports; there are no data on MOA.	Report of possible interaction comes from two case reports where isoniazid, rifampicin, and ethambutol were all administered during pregnancy.	(79)
Risedronate (Actonel, Atelvia): see Bisphosphonates				
Sarecycline (Seysara): see Tetracycline-class antibiotics				
Spironolactone (Aldactone, CaroSpir): see Potassium-sparing diuretics				
Sulfasalazine (Azulfidine, Azulfidine EN-tabs)	Folate	Sulfasalazine is a folate antagonist that can inhibit the reduced folate carrier and the proton-coupled folate transporter, decreasing intestinal absorption of folate.	Monitor folate status and consider supplemental folic acid if needed. Separating drug and folate intake may help prevent an interaction.	(159, 160)
Tetracycline-class antibiotics (chlortetracycline, demeclocycline, doxycycline [Acticlate, Avidoxy, Doryx, Doryx MPC, Doxy 100, Mondoxyne NL, Morgidox, Oracea, Soloxide, Targadox, Vibramycin], eravacycline [Xerava], lymecycline; omadacyclin [Nuzyra], oxytetracycline, sarecycline [Seysara], tetracycline)	Calcium	Calcium from food (e.g., milk) or supplements may decrease absorption of the antibiotic due to chelate formation in the intestine; absorption of calcium may also be decreased.	Separate antibiotic dose by 2 hours before or 6 hours after calcium intake from food or supplements.	(161, 162)
	Iron	Iron from food or supplements may decrease absorption of the antibiotic due to chelate formation in the intestine; absorption of iron may also be decreased.	Separate iron supplements from antibiotics by at least 2 hours.	(15, 162)
	Magnesium	Concomitant intake may decrease both drug and mineral absorption due to chelate formation in the intestine.	Separate antibiotic dose from magnesium-rich food or supplements by 2 hours or 4-6 hours after magnesium.	(15)
	Manganese	Concomitant intake may decrease manganese absorption due to complex formation in the intestine.		(15)
	Zinc	Concomitant intake may decrease both drug and mineral absorption due to chelate formation in the intestine. One small, cross-over study found that zinc sulfate did not inhibit absorption of doxycycline.	Separate antibiotic dose from zinc supplements by at least 2 hours.	(15, 161, 163, 164)
Thiazide diuretics (nadolol/bendroflumethiazide, chlorothiazide [Diuril, Sodium Diuril], chlorthalidone [Hygroton, Thalitone], hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone)	Calcium	Thiazide diuretics increase renal reabsorption of calcium and thus decrease its excretion.	If taken in combination with calcium supplements, thiazide diuretics may increase the risk of hypercalcemia.	(165)
	Magnesium	If taken for an extended period of time, high dosages of thiazide diuretics can interfere with renal reabsorption of magnesium, increase urinary excretion of magnesium, and result in magnesium depletion.	Monitor magnesium status (dietary, serum, and urinary magnesium) in patients on long-term therapy with thiazide diuretics.	(98-100)
	Potassium	Thiazide diuretics increase urinary excretion of potassium in a dose-dependent manner; their use may result in potassium depletion.	Monitor serum potassium concentrations in patients taking thiazide diuretics.	(166)
	Zinc	Thiazide diuretic use may inhibit zinc reabsorption in the distal tubule of the kidneys and thus increase urinary excretion of zinc, possibly decreasing zinc status.	Prolonged use of thiazide diuretics may increase risk of zinc depletion.	(142, 167, 168)
Torsemide: see Loop diuretics				
Trimethoprim (Primsol); Trimethoprim-sulfamethoxazole (Bactrim, Bactrim DS, Sulfatrim Pediatric)	Folate	Trimethoprim inhibits dihydrofolate reductase, which converts dihydrofolate to the active form of folate, tetrahydrofolate. Sulfamethoxazole inhibits bacterial production of dihydropteroate. Use of trimethoprim or trimethoprim-sulfamethoxazole may thus increase the risk of folate deficiency.	Inhibition of the bacterial enzyme by trimethoprim is thousands-fold more efficient than the mammalian enzyme; risk of folate deficiency increases with higher dosages of trimethoprim, especially when administered for prolonged periods. Measuring folate concentrations in red blood cells is a better indicator of folate status than serum folate concentrations. Supplementation with folinic acid (leucovorin) may reduce the antifolate toxicity.	(12, 169-172)
Valproic acid (Depakote, Depakote ER, Depakote Sprinkles)	Carnitine	Valproic acid may decrease carnitine status and lead to deficiency if the drug is taken for a prolonged period of time. Valproic acid interferes with L-carnitine biosynthesis in the liver and forms with L-carnitine a valproylcarnitine ester that is excreted in the urine.	L-carnitine supplements may be necessary in a subset of patients taking valproic acid. Risk factors for L-carnitine deficiency with valproic acid include young age (<2 years), severe neurological problems, use of multiple antiepileptic drugs, poor nutrition, and consumption of a ketogenic diet.	(173-175)
Verapamil (Calan SR, Verelan, Verelan PM)	Calcium	Calcium may decrease the hypotensive effect of intravenously provided verapamil.		(176)
Warfarin (Jantoven)	Vitamin C	Some evidence from case reports indicate that large oral doses might inhibit the action of warfarin.	Limit vitamin C intake from supplements to 1 g/day and monitor prothrombin time/INR.	(177, 178)
	Vitamin E	High-dose supplementation with vitamin E may inhibit vitamin K-dependent carboxylase activity, thus interfering with the coagulation cascade.	Evaluate use of vitamin E supplements due to an increased risk of bleeding.	(179)
	Vitamin K	Warfarin prevents recycling of vitamin K by antagonizing the enzyme, vitamin K oxidoreductase, thereby creating a functional vitamin K deficiency. Low dietary intakes of vitamin K can cause an unstable INR, and very high dietary (>150 µg/day) or supplemental intake of vitamin K may compromise the anticoagulant effect of warfarin.	It is generally recommended that individuals using warfarin try to consume the adequate intake for vitamin K (90 µg/day for women and 120 µg/day for men) and avoid large fluctuations in vitamin K intake that might interfere with the adjustment of their anticoagulant dose.	(180, 181)
	Boldo (*Peumus boldus*)-fenugreek (*Trigonella foenum-graecum*)	One case report of increased INR with co-supplementation of boldo and fenugreek while on warfarin therapy. MOA is not known. An active compound in boldo, baldine, inhibited aggregation of rabbit platelets *in vitro*. Fenugreek reportedly contains coumarin derivatives.	Interaction has been rated as 'highly probable' (182).	(183-185)
	Chitosan (*Swertia chirayita*)	Case report of increased INR with chitosan supplementation. MOA is unknown, although the authors of the case report state impaired absorption of vitamin K may be likely.	Monitor INR in those taking chitosan. Clinical studies are needed to determine if there is an interaction.	(186)
	Coenzyme Q_{10}	Coenzyme Q_{10} and forms of vitamin K are structurally similar.	Avoid coenzyme Q_{10} supplements in patients taking warfarin due to increased risk of blood clotting. If concomitantly used, assess prothrombin time/INR frequently, especially in the first two weeks.	(187)
	Cranberry juice	An increased INR has been documented in case reports (MOA not clearly explored), but no interaction has been found in controlled studies.	Monitor INR if patients consume cranberry juice.	(188-192)
	Danshen (*Salvia miltiorrhiza* root)	Case reports of increased INR and prothrombin time, possibly through effects on CYP450 enzymes. Results of a rat study indicate tanshinone IIA, a bioactive compound of danshen, binds to albumin and displaces warfarin, thus increasing blood concentration of warfarin and its effect. Inhibition of warfarin hydroxylation has also been shown in one rat study.	Avoid supplementation with herb.	(193-197)
	Compound Danshen Dripping Pill (CDDP; *Salvia miltiorrhiza*, borneol, and tanshinol)	A clinical study in patients with coronary heart disease with atrial fibrillation found CDDP had no effect on warfarin pharmacokinetics or pharmacodynamics.		(198)
	Devil's claw (*Harpagophytum procumbens*)	Report of purpura with co-administration of warfarin and devil's claw.	Little information is available in the published literature.	(199)
	Dong quai (*Angelica sinensis*)	Case report of increased INR with co-administration with warfarin. The herb contains coumarin derivatives.	Interaction has been rated as 'probable' (182).	(200)
	Echinacea	One small study in healthy men found co-treatment with echinacea and warfarin increased clearance and decreased plasma concentrations of (S)-warfarin, but did not affect INR or platelet aggregation. In a small, open-label study, echinacea had no effect on the metabolism of tolbutamide, which, like S-warfarin, is metabolized by CYP2C9.	Clinical studies are needed to determine if there is an interaction.	(188, 201)
	Fish oil	One case report of an interaction, but more recent studies have found no effect of fish oil supplementation on coagulation measures or bleeding incidence when co-administered with warfarin.	Monitor INR in patients taking fish oil.	(202, 203)
	Garlic	Garlic might enhance the anticoagulant effects of warfarin because of its antiplatelet properties. While two case reports have raised concern, clinical trials have found no adverse effects.	More research is needed to determine whether they are safe in patients on anticoagulant therapy. Closely monitor INR in patients taking garlic supplements.	(188, 204-206)
	Ginger	Case reports have suggested an interaction of high-dose ginger supplementation with warfarin. An open-label, cross-over study found no effect of ginger supplementation on platelet aggregation or INR in healthy individuals who were administered only a single dose of racemic warfarin (25 mg).	Clinical studies are needed to determine if there is an interaction.	(207-209)
	Ginkgo biloba	Several case reports of spontaneous bleeding with the use of the herb alone, but a meta-analysis of randomized controlled trials found no increased risk. Cross-over trials of its use with warfarin found no effects on INR and the pharmacokinetics or pharmacodynamics of warfarin or on INR.	Monitor INR if patients on warfarin are taking ginkgo extracts or supplements.	(209-212)
	Ginseng	One case report of decreased INR with ginseng supplementation (Ginsana, 3 times per day; dose not stated). One clinical study found American ginseng decreased INR after two weeks' supplementation. Other clinical studies have found no effect of Korean ginseng root or Korean red ginseng on INR, warfarin pharmacokinetics, or warfarin pharmacodynamics.	More research is needed. Monitor INR if patients on warfarin take ginseng supplements.	(213-216)
	Grapefruit	One case report of a possible interaction; a small clinical study found no effect of grapefruit juice on prothrombin time or INR.	Clinical studies are needed to evaluate whether there is an interaction.	(217, 218)
	Green tea	Green tea is a source of vitamin K. Consumption of large amounts of green tea could decrease INR.	Avoid large amounts (>0.5L per day) of green tea. Patients taking warfarin should have consistent dietary intake of vitamin K intake and avoid large fluctuations.	(219)
	Mango	Case report of 13 older men with increased INR following mango consumption. MOA is not known but hypothesized to include inhibition of CYP2C19 by vitamin A.	Interaction has been rated as 'highly probable' (182).	(220, 221)
	Papain from papaya	Papain intake may increase INR, e.g., may increase bleeding by harming the integrity of the mucosal membranes of	Only one case report. Avoid supplementation with papaya extract; encourage eating fresh papaya instead.	(199)

		integrity of the mucosal membranes of the GI tract. However, the exact mechanism is unknown.		
	Pomegranate (*Punica granatum*)	One case report of increased INR with high intake of pomegranate juice. Pomegranate juice has been found to inhibit CYP2C9 activity *in vitro*.	Clinical studies are needed to evaluate whether there is an interaction.	(222, 223)
	Psyllium (*Plantago ovata*)	Psyllium supplements may slow and decrease intestinal absorption of warfarin if taken concomitantly.	Separate taking psyllium supplements and drug by at least 2 hours.	(15)
	Resveratrol	Resveratrol inhibits platelet aggregation *in vitro*.	Supplemental intake could theoretically increase the risk of bruising and bleeding when taken with warfarin.	(224, 225)
	Soy protein	One case report of a decreased INR in a patient taking warfarin following consumption of soy milk. MOA is unknown.	Monitor INR if the patient adds or eliminates soy protein from diet.	(226)
	St. John's wort (*Hypericum perforatum*)	Use of St. John's wort has been shown to induce various CYP450 enzymes, increasing warfarin clearance and decreasing INR.	Closely monitor INR.	(216)
	Sweet clover	Interaction might be possible since the herb contains coumarin derivatives.	Human reports are lacking.	(227)
	Turmeric (*Curcuma longa*)	Curcumin from turmeric has been found to inhibit platelet aggregation *in vitro*, thus curcumin supplementation could theoretically affect risk of bleeding in patients taking warfarin. A small pilot study found no effect of the curcumin formulation, Meriva®, on INR.	Clinical research is needed to determine whether curcumin supplementation interacts with warfarin.	(228, 229)
Zoledronic acid (Reclast): see Bisphosphonates				
US brand names listed in parentheses. *Abbreviations: INR, international normalized ratio; MOA, mechanism of action*				

Table 2. Suggestions for Further Reading

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